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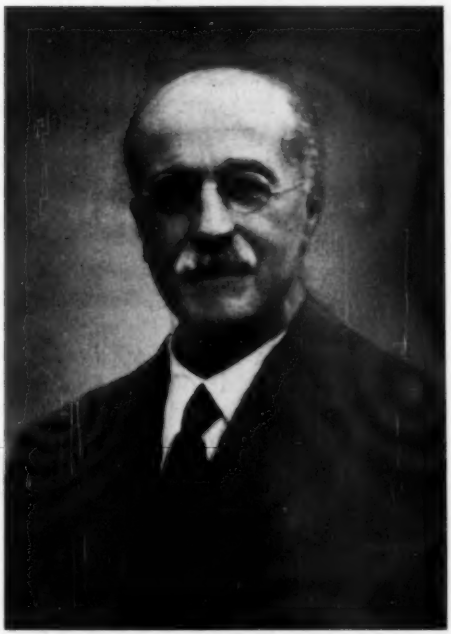

ALFRED ERNEST BARCLAY

In Memoriam

One of the oldest pioneers in radiology in England, well-known and highly esteemed throughout the world, Dr. A. E. BARCLAY, died at his home in Oxford on April 27, after a year of increasing illness, at an age of nearly 73 years. In Nov. 1946, he underwent operation for a pyloric cancer, but made an amazingly quick recovery and could soon resume his work. His health was, however, impaired by some attacks of pneumonia followed by bronchiectasis. In the summer of 1948, symptoms of intestinal obstruction appeared, necessitating a second operation which revealed an evidently malignant intussusception in the caecal region.

During the following months, his strength perpetually declining, he was obliged to spend most of his time in bed, but his brain was active and he pursued his work to the last with an amazing energy.

BARCLAY was educated at the Leys school and at Christ's College in Cambridge. After clinical studies at the London Hospital, he graduated in 1904. Already as a student, he grew interested in radiology, seeing its immense scope for medicine. In 1906, he returned to his native town, Manchester, where he started as a private radiologist; soon he became attached to Ancoats Hospital and lecturer in radiology at the Manchester University. From these early years, he has given a vivid and expressive account, spiced with his quiet humour. At his arrival, there existed in Manchester only one roentgen apparatus, housed in the gallery of an old hospital chapel without windows or ventilation. It was run by a firm of chemists who managed all the roentgen practice in the city, the interpretation of the plates being done by surgeons or physicians. BARCLAY had to build up literally everything. At Ancoats the first real roentgen department was started and here he made his first experiments with the bismuth meal in gastric diseases. In 1909, he was appointed radiologist to the new-built Royal Infirmary where, though, no space was provided for roentgen service. Eventually, he was allowed to take over a basement which during many years had to serve all the needs of roentgen, electrotherapy and massage. It was not till 1918 that BARCLAY was elected to the honorary staff, and from that moment his position thoroughly improved.

In spite of these difficulties, BARCLAY had found time to publish some papers on gastric radioscopy as well as a short text-book on Roentgen Diagnosis and Treatment which marked an era in English radiology (1912). During the war 1914—18 he served as a captain and radiologist at a Manchester military hospital where he had ample opportunity to teach roentgen diagnosis to his younger colleagues and where he devised an ingenious instrument for localizing and extracting foreign bodies. His old interest in university teaching was now awakened. Compelled by the fact that no systematic training in radiology existed in England, he succeeded, together with ROBERT KNOX and STANLEY MELVILLE, in persuading the Cambridge University to set up a diploma in radiology, and at about the same time these three champions brought about the fusion of the British Institute of Radiology with the older Roentgen Society, thereby establishing a broader and more suitable organisation of radiological science. Further, it was mainly through the initiative of the same men that the first International Congress of Radiology could take place in London 1925.

In 1927, BARCLAY was appointed lecturer in radiology at Cambridge, this post then being vacant. This step certainly meant a sacrifice in view

of his extensive clinical work in Manchester, but he did not hesitate to take it to preserve the continuity of radiological teaching and the maintenance of the Cambridge diploma. He was an outstanding teacher and a very skilful deviser of all sorts of apparatus, among others a cinematographic camera for studying the non-propulsive movements of the colon. In this situation, notwithstanding poor accomodations, he stayed until 1937 when the Cambridge diploma was cancelled, other universities having undertaken the training in radiology. Surely, it was with satisfaction that he now accepted the invitation of Dr. K. J. FRANKLIN to join him as honorary radiologist at the Nuffield Institute for Medical Research in Oxford.

During the twenties and his Cambridge years, BARCLAY pursued his diagnostic studies on the alimentary canal and published numerous papers in this field. His results he gathered in the extensive book »The Digestive Tract» (1933), being perhaps not a text-book in the ordinary sense, but a collection of lectures and articles of technical, anatomical, physiological and pathological contents, touching upon every part of the digestive system, very personally written and quite on a level with the period. This work was for years a source of information to English radiologists, containing original investigations as well as numerous statements and precepts of general value even for our own age.

In the field of therapy, BARCLAY's only clinical contribution is a paper on the treatment of hyperthyroidism (1927), a record of 300 cases. His technique and results are very much the same as in the Scandinavian countries at that time, and he followed his cases up for several years.

The outbreak of the second world-war meant an interruption of BARCLAY's scientific work, the Ministry of Health having appointed him adviser with the immense responsibility of the organization and supervision of all radiological service in the enormous emergency hospital scheme, comprising about 200,000 new beds in all parts of England. During the first year, he personally visited every hospital, getting an intimate and invaluable knowledge of persons and hospitals.

The last 12 years of his life, BARCLAY devoted to an intensive scientific work at the Nuffield Institute where he had found a scope for his active and ingenious brain that suited him perfectly. As a trained radiologist with great experience in roentgen cinematography and -micrography he became an important partner in several team researches of interesting and even sensational character.

Together with FRANKLIN and MACBETH, he studied the ability of ciliary movement to remove alien dust from the bronchioles after insufflation into the lungs (1937—38, continued in 1940 with definitive results).

During the same years, BARCLAY in collaboration with FRANKLIN,

BARCROFT and BARRON was occupied in studying the foetal circulation in the great vessels and the heart before and after delivery, including various problems, such as the identification of the ductus arteriosus, the time of its functional closure and the closing mechanism, the time of closure of the foramen ovale and the pulmonary circulation before and after closure of the ductus arteriosus. These experiments were made on sheep foetuses, delivered by caesarian section, using the cinematographic camera described in detail in the Brit. Journ. of Rad. 1940.

Then followed the brilliant research on the vascularisation of the kidney, performed in 1945—46 by TRUETA, BARCLAY, DANIEL, FRANKLIN and PRICHARD and based on the idea advanced by TRUETA that the renal anoxia found in certain pathological conditions seemed to be caused by an overstimulation of the vascular nerves. The authors have stated that on various types of nerve-stimulation, with the abdomen unopened as well as in laparotomized animals, the renal blood-flow may be diverted from its normal course through the cortex to passing exclusively to the subcortical plexus and the medullary vessels, thus establishing a short-circuit. These results were obtained mainly by microarteriography and confirmed by experimental injections with various contrast media showing the vascular pathways. These investigations were published in the extensive work »Studies of the Renal Circulation» (1947), a most brilliant and clear-sighted report, the far-reaching implications of which can hardly be overestimated.

As a consequence of this research, BARCLAY in collaboration with the surgeon BENTLEY, sought and found evidence of a similar shunt mechanism in the gastric wall. Microarteriography of injected specimens from cadavers had shown a complete filling of the mucosal vessels, whilst in operated specimens they regularly remained empty. The surgical trauma here evidently acts as a nerve stimulus, causing arteriovenous pathways in the submucosa to open, this effect being demonstrated by the venous blood changing its colour into pink and its oxygen saturation increasing from 74 % to 91 %. By blocking the sympathetic gastric nerves before operation, the shunting effect was prevented and the mucosal vessels were well filled out.

These results led BARCLAY to the conviction that such shunt mechanisms exist in most organs of the body and that nature provides a twofold way of controlling their functions, viz. by increasing and diminishing the blood supply by way of these shunts, and secondly by direct control of cellular activity. »I suspect she uses the vascular method by choice and holds direct control in reserve for occasions when it is inconvenient to use vascular control.» (Private letter to the author.)

One more discovery of a surprising kind BARCLAY made in the field of botany. By way of experiment, he made microradiographs of leaves

of plants and shrubs and was amazed to find »spots» of high atomic material travelling up from the ground and lined up in the sap channels of the stems and strewn about in the venules of the leaves — a finding quite unsuspected by botanists. This detection seems to be of great interest to botany, especially to agriculture.

In the beginning of this year, BARCLAY, in order to escape the Oxford climate, went to Torquay, bringing with him his microradiographic apparatus and putting up a laboratory at his hotel. He was too ill to leave his bed, but managed to make one last interesting observation, namely that of intracellular deposits of haematite in the lungs of an iron-miner. In spite of his weakness, he invented on this occasion an ingenious vacuum cassette, by which the air absorption between the beryllium window of his tube and the film could be eliminated.

The writer has known ALFRED BARCLAY for nearly 25 years. To know him was inevitably to love him, and in the course of time our friendship grew intimate. The war made personal meetings rare, but he was an excellent correspondent and his letters bear witness of his never failing attachment unto the last. Nothing could be more agreeable than spending the days in his home where his gay humour was flowing and his and his wife's amiability and kind consideration knew no bounds. In his younger days, he was an extensive traveller, finding innumerable friends where he went, in Europe as well as in U. S. A. and Australia. His devotion to radiology and the methods of its development was fervent, he was endowed with a lively gift of imagination and high technical skill. With amazing energy he pursued his problems even when confined to bed. Despite his delight in his researches and their happy results, he received official recognitions with the greatest modesty, detesting high phrases and outward formality. He was keenly interested by music, and in his younger days he took an active part in the musical life in Manchester. During the last war, he and his wife gathered in their home American soldiers for musical entertainment. An evening concert chosen from his large collection of grammophone records cf classical music was an outstanding pleasure. Fishing was the sport he preferred. He had outstanding mechanical gifts, and the workshop was his main hobby. He loved flowers and had a delightful garden.

Though knowing his time to be short, he kept his optimistic mind as long as possible, speaking but little of his physical pain. During his last months, he occupied himself in writing a book on radiological methods as applied in research. It will appear as his very last contribution to the science he loved. He faced death bravely and died as a hero, literally in harness. Of the deep religious earnest of his character the closing words of his Silvanus Thompson lecture bear witness:

»We may study the stars in their courses and discover that God

thinks in mathematical terms; we may disprove all we thought and dreamed of religion, and yet we are no nearer realizing what God is or of what life is. Our knowledge, our most intimate knowledge, only touches the fringes of the great curtain that hides God and the living miracle of life.»

In 1906, BARCLAY married MARY FARLANE who throughout his life was a faithful and interested companion in his work and a lovely hostess in his pleasant home. To her goes an equal share of the gratitude felt by his friends.

Of course, BARCLAY received a great many marks of honour and esteem from his colleagues in different countries. He was President of the section of Radiology of the Brit. Med. Ass. at Cambridge in 1920 and at Melbourne in 1930, President of the Roentgen Society in 1924 and of the Brit. Inst. of Radiology in 1931. That year he was also appointed Silvanus Thompson Lecturer, and he was to have delivered the Mackenzie Davidson Memorial Lecture in March 1949, had not his illness made it impossible; but he received the Lecturer's medal in his bed. In 1935 he became a member and in 1941 a fellow of the Royal College of Physiology, in 1948 a fellow of the Faculty of Radiologists. In 1937 Oxford conferred on him the D. M. degree and in 1947 the honorary degree of D. Sc. Since 1925 he was honorary fellow of the American College of Radiology and he held the same honorary fellowship also of the Radiological Society of North America, of the Northern Association for Medical Radiology, and of the Australian and New Zealand Association for Radiology.

Lars Edling.

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(HEAD: PROF. O. REUTERWALL)

ESTER SULPHURIC ACIDS IN STROMA CONNECTIVE TISSUE[1]

by

Bengt Sylvén

Introduction

Growth of fibroblasts was found to be associated with the presence of high molecular polysaccharide ester sulphates (ES). These substances form an ES-protein complex, which is demonstrable both during new-formation of fibroblasts (6, 7) and mesenchymal tumor cells. Further investigations indicate the presence of same or similar substances in the stroma and in the intercellular medium of growing epithelia. Normal (8) and cancerous epithelia are found to induce a non-specific stroma reaction which is characterized by considerable amounts of ES. Attention is consequently focussed to the functional interactions between growing epithelia and their connective tissue matrix.

The ES-protein complex mentioned above presents an intense, bright red metachromasia, which is alcohol resistant. The cytoplasm of growing epithelia generally show a metachromasia of lower intensity with a lower alcohol resistance. This may indicate the presence of an ES complex of another type in epithelial cytoplasm, or perhaps some other substances. Now, the point is that all types of rapidly growing epithelia, both normal and malignant, are found to induce the appearance of ES in their intercellular matrix, and this occurs whether a simultaneous new-formation of stromal fibroblasts coincides or not. Similar ES have so far not been observed in relation to quiescent epithelia.

Material and Methods

A large number of normal and tumor epithelia (Table 1) have been collected from animal and human sources in order to obtain series of epithelia with different growth

[1] Read before the Fourth International Cancer Research Congress, St. Louis, Missouri, September 4, 1947; submitted for publication, April 30, 1949.

capacities. Methods used in this study are essentially similar to those previously described (9).

Table 1.

Tabulation of Material and Main Results

Type	Origin and state	Approx. amounts of ES-protein complex present in the	
		Stroma and Intercell. medium	Cytoplasm of epithelia
Normal quiescent epithelia	Skin, hairs, glands	0	0
Simple regerations not combined with growth of stroma	Epidermis, growing	+	+
	Hairs, »	+++	(+)
	Mucous membranes, growing	+	(+)
Organoid regeneration	Endometrium in prolifer. phase	+	0
Epidermal hyperplasias	Growing	+	(+)
	Quiescent	0	0
Benign epithelial new-growths (papillomas, etc.)	Growing	+−++	(+)
	Quiescent	0	0
»*Precancerous*» *conditions* of skin and mucous membranes	Growing	+−+++	+
	Quiescent	0	0
Primary human carcinomas; all types, 1,100 cases investigated	In growth zones	+−+++	+
	Areas not growing	0	0
Metastatic human carcinomas; 100 cases investigated	In growth zones	+−+++	+
	Areas not growing	0	0
Transplanted animal tumors; Jensen, C. 2146, C. 27, and Flexner	In growth zones	+	+
	Areas not growing	0	0

Results

This report embodies the main results obtained in this laboratory up to 1947. For lack of more detailed qualitative and quantitative data the statements have to be considered as rough expressions of complex series of events, which so far can merely be surmised in principle. Much remains to be done before full interpretation will be gained.

Simple epithelial regeneration. — When the regeneration of stratified epithelium is accelerated moderate amounts of metachromatic ES-protein complex appear along the stromal border-line, in the intercellular spaces, and in the cytoplasm of growing epithelia (7). Unpublished investigations (SYLVÉN) on the hair cycle of the albino rat clearly indicate, that large amounts of ES are demonstrable in the connective tissue papilli only during stages of intense growth of hair epithelia. Parallel to the decreasing growth rate a falling gradient of ES was found, until the metachromatic reaction of the papilli was completely abolished following

cessation of growth. These findings show that high molecular sulphurous compounds are stored in the stromal matrix and transferred to the cytoplasm of epithelia during the isolated growth of normal epithelium. The results indicate a striking conformity with the distribution of alkaline phosphatase in the hair follicles (2). The results may also have bearing on the supply of sulphur for the synthesis of eukeratins.

Organoid growth of non-cancerous epithelia. — This group comprises conditions characterized by simultaneous new-formation of both epithelia and stroma connective tissue, and has thus some characteristics in common with the carcinomas. The growing stroma connective tissue is always metachromatic. In selected cases almost pure epithelial growth is found, and then pictures are seen identical with those just described in epithelial regeneration (8).

Carcinomas. — In all common human carcinomas (Table 1), the growing cancer vegetations primarily induce a pronounced *transformation* of the surrounding adult connective tissue. In this way a gelatinous matrix becomes established, which presents the following characteristics:

Dedifferentiation. — Connective tissue fibrils are gradually dissolved and transformed into a protein gel.

Cytology. — Fibroblasts are swollen, with ballooned faintly basophilic nuclei, poor in chromatin. They have often distinct nuclear membranes, and big nucleoli.

ES-protein complex. — Varying amounts of metachromatic material, apparently forming an ES-protein complex, are found in the intercellular matrix.

Mast cell alterations. — A depletion of metachromatic material from the mast cells is uniformly found in such transformed stroma regions, indicating local loss of ES from mast cytoplasm. Cytological examinations reveal that mast cells cannot keep up their normal cytoplasmic functions.

This transformation process means that a uniform soil is established for epithelial as well as fibroblastic growth. If no epithelial growth occurs, this gelatinous matrix will in time redifferentiate, and reattain the normal adult shape and state of balance. But actually, this does not generally happen in carcinomas. The gel is instead treated in different ways according to the varying capacities of the cancer cells. We are now facing a second process, which seems of prime importance to the fate of the matrix mentioned above, namely the *disintegration and digestion* of the constituents of the gel. It was found, that the amount of ES demonstrable in the growth zones of different carcinomas is a function of growth rate and graded malignancy of the individual tumors. Thus, the growing cancer cells digest and consume the constituents of their tumor bed, and this reaction evidently runs with different velocities, which will explain important features of the individual stroma reactions, as characterized below.

Carcinomas of low growth rate:

Transformation process pronounced
Low capacities for digestion of matrix
Large amounts of ES-protein complex demonstrable
Marked desmoplastic properties

Carcinomas of moderate growth rate:

Transformation process increased
Increased capacities for digestion of matrix
Moderate amounts of ES-protein complex demonstrable
Desmoplastic properties insignificant

Carcinomas of high growth rate:

Transformation process very rapid
Rapid digestion of matrix
Small amounts of ES-protein complex demonstrable
Desmoplastic properties absent or very low

The rough correlation between growth rates and demonstrable amounts of ES-protein complex suggests that this substance is consumed or subjected to disintegration in the course of the digestion process just outlined. This interpretation will elucidate part of the mechanisms operating during infiltrative-destructive growth of carcinomas (cfr. 9). Cytological examinations indicate that quite a number of fibroblasts degenerate and present a nuclear cytology similar to that seen in the excessive B-type of cancer cells (2). Later on, such fibroblasts are digested, and then nuclear constituents may be transferred to the gel, and will be accessible for growing cells.

Judging from examinations of early human carcinomas, some transplanted animal tumors (Table 1), and the different stages of experimental skin carcinogenesis (unpublished), the appearance of ES-protein complex is simultaneous with a depletion of metachromatic material from mast cell cytoplasm. This supports my suggestion that the ES are derived from the tissue mast cells (6, 9), and consequently the chemical composition would reasonably be similar to that of native heparin.

May I stress that these ES are *only* found in close relation to actually growing cancer cells. They are never seen in degenerating tumor areas, which indicates that common conceptions regarding the occurrence of »mucinous» and »myxomatous» degeneration of cancer stroma have to be rejected (cp. 9). Factors known to interfere with growth, such as inflammatory alterations and treatment with roentgen or radium (gamma rays), have been found to provoke a disappearance of the ES-protein complex and an increasing differentiation of the gelatinous stroma.

Discussion

Present results indicate the existence of very close functional interactions between growing epithelia and stroma, probably aiming at the supply of raw-materials for epithelial growth. The transfer of high molecular ester sulphates to the cytoplasm of epithelia is an expression of such a stroma function. Some suggestions should be made as to the operating factors. In terms of biochemistry the transformation process mentioned above means, that the normal ultrastructure of adult collagenous fibrils is broken up. This might be accomplished by depolymerizing enzymes (»collagenase»?). The subsequent digestion process seen in carcinomas can hardly be effectuated by other means than by proteolytic enzymes. Continued research on the regional distribution of pertinent enzymes will elucidate these matters.

Interpretations are greatly hampered by the present lack of chemical and enzymal data applicable to the growth zones in tumors. The composition of the ES under question is not yet known, and therefore their biological rôle can hardly be discussed (cfr. 6, 7, 9). Tempting speculations may be presented with bearing on growth problems in general. If we calculate with heparin molecules in the intercellular medium of growing tissues, particular interest will be paid to the possible inhibitory effect of heparin on depolymerizing and proteolytic enzymes. The interference by heparin on such enzymes would pertain to the modern theory of RITTENBERG and SHEMIN (5), who believe that growth is the result of inhibition of proteolysis. Considering the possible disintegration of the heparin molecule, bearings would be obtained to the rôle of sulphate, glucuronic acid, and glucosamine. Tissue mast cell cytoplasm also contains enzymes, such as alkaline phosphatase (4), which give further connections with pertinent growth problems. Recent papers call attention to metachromatic material in yeast cells (3, 10, 11). It may be recalled, however, that the volutin granules in yeast do present an alcohol resistant metachromasia,[1] and thus the presence of ES has to be postulated.

The results reported above open new aspects to the study of functional interactions between growing epithelia and their nutrient matrix so far the transfer of polysaccharide ester sulphates is concerned, and these aspects have further a bearing on growth problems in general.

SUMMARY

Growing epithelia, both normal and cancerous, induce the appearance of metachromatic polysaccharide ester sulphates in the stromal matrix, in the intercellular medium, and also to a variable extent in the cytoplasm of the epithelia mentioned above. The origin and functional significance of this group of substances are briefly discussed.

[1] Unpublished re-investigations by the author.

ZUSAMMENFASSUNG

Sowohl normale als auch maligne, wachsende Epithelzellen verursachen ein Auftreten von sich metachromatisch färbenden Polysaccharid-Estersulfaten im Stromabindegewebe, in dem interzellulären Medium und in wechselndem Masse auch im Zytoplasma der erwähnten Epithelzellen. Die Herkunft und die funktionelle Bedeutung dieser Substanzengruppe wird kurz erörtert.

RÉSUMÉ

Tant les cellules épithéliales normales que les malignes, au stade de la croissance, provoquent l'apparition d'acides-esters polysaccharido-sulfuriques colorables métachromatiquement, et cela dans le tissu conjonctif du stroma, dans le milieu intercellulaire, et même, à des degrés divers, dans le cytoplasme des cellules épithéliales dont il était question plus haut. L'auteur discute brièvement de l'origine et de la signification fonctionnelle de ce groupe de substances.

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FROM RADIUMHEMMET, STOCKHOLM, SWEDEN (HEAD: PROFESSOR ELIS BERVEN)

THREE CASES OF IRRADIATION INJURIES[1]

by

Sven Hultberg

During the past 20—25 years the use of roentgen and radium rays has increased considerably, not only within human and veterinary medicine and odontology. Also in various branches of scientific research and education, as well in the technical and commercial fields, irradiation is utilized to a growing extent and, this should be particularly noted, by a growing number of people who are insufficiently informed of the biological and cumulative effect of irradiation. In proof of the enormous increase in the use of radium and roentgen, mention may be made of the fact that (according to SIEVERT, 1947), the number of those engaged, in some form or other, in irradiation in Sweden amounted, in 1920, to one in ten thousand while, at the present time, the corresponding figure is one in a thousand of the population. It is therefore, as a matter of course, indispensable to pay the strictest attention to the question of protection against irradiation injuries and the various problems pertaining to that subject.

From the earliest days of radiology it has been well known that roentgen and radium, when not handled with due care, may cause more or less serious injuries. At that time such injuries could be ascribed, partly, to a lack of knowledge of the necessity of an effective protection against the rays and, partly, to the inferior technical means then available. — Still, in spite of our present familiarity with the risks that a careless manipulation of roentgen and radium irradiation involves and, further, in spite of our present technical means of providing a proper protection, we notice but too often evidence of a certain levity in dealing with these rays, a levity that has to be grimly paid for. — That this unconcern in connection with irradiation is a fairly common thing is obvious, inter alia, from a warning issued, in 1942, by the Ministry of Health in England, entitled »Emergency of Medical Services». There stress was laid on the necessity of carefully observing such directions as had been published. To that paper I shall again refer below.

[1] Submitted for publication, May 2, 1949.

During the past years, at Radiumhemmet, we have had to treat several cases of irradiation injuries. From various points of view, three of these, in particular, are of a general interest and, therefore, worthy of special attention. The injuries illustrate different aspects of the use of roentgen irradiation.

1. The first of these three patients (hospital record number 10752/1946) was a young, unmarried woman, born in 1920. In the summer of 1945 she became pregnant after coitus with a roentgen technician. Both had been called up for service at a military hospital during the armed preparedness. The patient had no previous experience of roentgen work. Her last menstruation occurred at the end of July 1945. When her male companion was informed of this, he told her that he was married, suggesting, at the same time, abortion. The patient, however, felt disinclined to this. According to her own statement the roentgen technician had, nevertheless, later returned to his proposal stating that he could »help» her in a novel and riskless way. At the beginning of October 1945 the patient was then exposed to a roentgen irradiation of the hypogastrium. It was administered by means of a roentgen tube, belonging to a photofluorography apparatus. The patient stood with her clothes on, pressing the lower part of the abdomen against the roentgen tube, the exposure lasting for about 5 minutes. — At the end of October this treatment was resumed in the same manner. — About the middle of November the patient noticed a beginning redness in an area, about the size of a child's palm, just below the umbilicus. This redness grew more and more intense. Gradually a blister formation arose and, about Christmas 1945, a wound that did not show any tendency to heal. — Meanwhile, the pregnancy proceeded, and on the 30th of March 1946 the patient gave birth to a child, weighing 2 kg. The partus occurred 15 days before expected time. — After the delivery the wound began to feel more and more painful. The skin round it seemed thickened, and became sore. At the end of April 1946 the patient applied to a doctor who referred her to a hospital in her home district. After some time she was transferred from there to Radiumhemmet where she was admitted on the 27th of June 1946.

The general condition of the patient was good. In the abdominal wall immediately below the umbilicus a firm infiltrate of about 7 × 9 cm was found. Within the lower part of this infiltrate, an irregularly formed ulceration, the size of 3 ½ × 6 cm, was noticeable, with loose, necrotic granulations at the bottom (Fig. 1). The skin surrounding the wound was pale and atrophic with telangiectasias and pigmentation of the edges. The infiltrate was palpable deep down, being fixed to the abdominal musculature. Biopsy disclosed changes typical of an irradiation necrosis. No evidence of a tumour or any specific inflammation was ascertainable. — To begin with, the patient was treated conservatively with incitamin fomentations. However, since after two months only an inconsiderable tendency towards healing was observable, I performed, on 21st of August 1946, an electroexcision of the wound with coagulation of its bottom. A supplementary intervention of the same sort was made on the 7th of September 1946 (Fig. 2). It appeared that the injury extended down into the exterior muscular fascia. The latter was, however, left intact at the intervention. In the course of the following months the wound healed, and after a lapse of half a year the healing was complete. At check-ups, on the 17th of October 1947 and on the 17th of June 1948, the patient displayed a radiate cicatrix. She had no subjective troubles (Fig. 3). Her menstruations were regular, but scanty, with a duration of but 36 hours. Apart from a moderate anemia, with hemoglobin 75 per cent and red blood corpuscles 3.9 mill. at the time of the admission of the patient, no effect on the blood could be found. The number of white blood corpuscles and the differential count proved normal. No damaged blood corpuscles were detectable. For this reason, the anemia is not very likely to be an irradiation effect.

Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1, 2 and 3. Irradiation injury, photographed 8 months after the occurrence, after electrocoagulation, and as healed.

As far as the child is concerned, the patient has stated in a letter, that her son has an unusually small head for his age. It has grown, but not proportionately to his body. He began to sit up at 10 months of age and to crawl when he was 18 months. He took his first steps when 2 years and 3 months old. Only at the age of about 2 years and a half he began to speak, though so far uttering but single words. Otherwise, he does not in any

way give the impression of being apathetic. On the contrary, he is keen and curious about everything near him. — As yet it is, however, probably too early to say whether the boy has suffered any serious harm from the irradiation, or whether this constitutes the cause of his apparently belated development.

Because of the lack of judgment of her male partner and, more especially, his reckless use of the roentgen apparatus (at which, when used for diagnostic purposes, he had previously assisted as a technician) about 18 months of physical sufferings have been inflicted on this poor young girl. The psychic trauma to which the patient has fallen a victim — not least from her constant anxiety about potential radiation injuries to her child — forms an important part of her story.

2. The second case concerns a male doctor, born 1905 (hospital record number 17005/1946). In 1938, the patient served as an assistant doctor at a department for roentgen diagnosis and, in 1939, at a radiotherapeutic department. In 1941—42 he worked, for two periods of two months each, as a roentgenologist at a military hospital. Otherwise he was, during the years 1940—46, engaged in surgical work.

From the 2nd of September to the 22nd of November 1946 the patient had, on 7 different occasions, performed cryptoscopic screenings, in order to control the reductions of serious fractures, according to the following schedule:

1) Fractura radii sin.: On the 2nd of September 1946: repeated fluoroscopies were made of 3—10 seconds each, about 30 seconds in all. On the 2nd of October 1946 two screenings of 3—10 seconds each took place. Althogether the fluoroscopies comprised about 30 seconds.

2) Fractura supracond. humeri dx.: On the 4th of October 1946 two screenings, of 3—5 seconds each, were performed. On the 5th of October the examination was repeated. The total amounted to 30—45 seconds.

3) Fractura supracond. humeri sin.: On the 12th of November 1946 repeated fluoroscopies of 2—15 seconds each were undertaken, a total of, say, about 45 seconds. On the 15th of November they were resumed, each time comprising approximately 3—10 seconds, or about 30 seconds in all.

4) Fractura malleolar. lateral. et medial. et proc. post. tibiae sin.: On the 22nd of November, two screenings took place of 3—5 seconds each, a total of about 20 seconds.

While engaged in this work the patient used neither lead rubber gloves, nor any lead rubber apron. On one occasion his reason for not doing so was that, owing to the wounds, he was forced to work under sterile precautions. At the fluoroscopies no reduction, only checking of the position of the fractures, was performed. This method was resorted to, because of the fact that a satisfactory reposition in the ordinary way, by means of roentgen photographs, had proved unfeasible. The total irradiation time in this case did not exceed 4 minutes. The roentgen apparatus in use was of a small, transportable type, designed for 55—60 kilovolts and 4 milliamperes at fluoroscopy and 10 milliamperes at exposure. — As early as on the 23rd of November 1946, *i. e.* the day after the last screening, the patient felt itching and heating in the finger-tips of the right hand. On the 24th of November he noticed a swelling and redness that continually increased. On consultation, a dermatologist diagnosed an acute dermatitis. Only some days later it became evident that a roentgen injury was indicated. On the 2nd of December 1946 the patient was admitted to Radiumhemmet. He then showed redness and a swelling on the three middle fingers of his right hand and a beginning blister formation on the dorsal side of the fingers, par-

Fig. 4. Fig. 5.

Figs. 4 and 5. Roentgen injury: ten days after the beginning of the irradiation reaction, and after the lapse of an additional 2 months.

ticularly pronounced on the middle finger. The proximal limit of the blister formation was on a level with the interphalangeal joint (Fig. 4). During the following days the blister formation continued to develop. A slight redness could be noticed also on the thumb and little finger. However, on these fingers no blister formation appeared. The treatment was conservative, with protective bandages with powder, alternating with indifferent ointments and, several times each day, fomentations with an infusion of chamomile. The reaction visible on the middle finger was particularly marked, displaying an ulcerous dermatitis with a bleeding wound surface. At the middle of January 1947 all the fingers had healed. At that time, however, the nails of the three middle fingers had fallen off (Fig. 5). The blood picture disclosed a certain affection with a moderate leukopenia, a relative lymphocytosis (52.5 per cent) and some split and fringed nuclei among the monocytes. The sedimentation reaction was normal. — After half a year the blood picture was again normal.

The first impression is one of astonishment at the fact that a few fluoroscopies were able to cause acute injuries of such a serious type. — Also one of the patients under treatment had shown an irradiation injury on his elbow. — However, a close examination of the roentgen apparatus that had been used, and of the circumstances on the occasion of the screenings, disclosed that the roentgen tube lacked an extra filter, as well as a limiting cone. The apparatus filter corresponded to 0.5

Fig. 6. Roentgen injury: about 1 month after the beginning of the irradiation reaction.

mm Al. The distance from the focus to the skin had, as a rule, been about 20—30 cm, though the patient may very likely, on several occasions, have dipped his hand down towards the tube, there being, as stated, no cone to prevent such an »approach». — It is difficult to form a correct estimate of the roentgen dose that affected the fingers of the patient, but it probably corresponds to a single dose of 800 to 1,000 r.

After the primary healing in February 1947 the patient was fit for work up to October of the same year. In the course of a plastering he accidentally scratched the thin skin on the dorsal side of the right middle finger, obtaining a wound that refused to heal, but rather increased in size, causing a severe ache. Only after a conservative treatment covering several months, with fomentations of various kinds, inter alia with a penicillin solution, and bandages with various indifferent ointments and sulfa powder, the wound gradually healed.

The skin on the three fingers now reveals an atrophy with telangiectasias. The nails are partly defective, but the patient is perfectly fit for work and able also to perform surgical interventions.

To sum up, this case relates to a physician who, owing to a series of unfortunate circumstances, originating from an apparatus unsuitable

Fig. 7. Fig. 8.

Figs. 7 and 8. Epilation in spots of the right temporal region, owing to roentgen irradiation. The hair growing again, 4 months later.

for its purpose, became the prey of a serious injury, while engaged in his duty to help patients with complicated fractures, difficult to reduce.

Also to us in Sweden, this case brings home the importance of the above-mentioned memorandum which the British Ministry of Health, in 1942, circulated to all the hospitals in their country. The following is an extract from that paper:

»1) It is necessary to stress again the risks attaching to use of a roentgen fluorescent screen during the settings of a fracture or the removal of a foreign body. The use of films is far safer and more accurate.

2) If in spite of the risks screening is deemed essential in exceptionally difficult cases, the roentgen apparatus should be operated by the radiologist; cones or cylinders to limit the roentgen field should be used.

3) The operation of the roentgen apparatus by the surgeon himself is to be deprecated. This should be in the hands of a skilled operator, who not only controls the radiographic technique but also safeguards the surgeon from unnecessary risks.

4) The cryptoscope is a very dangerous device and should never be used.

5) Since operating conditions vary in different hospitals, the responsible surgeon should collaborate with the radiologist in drawing up a

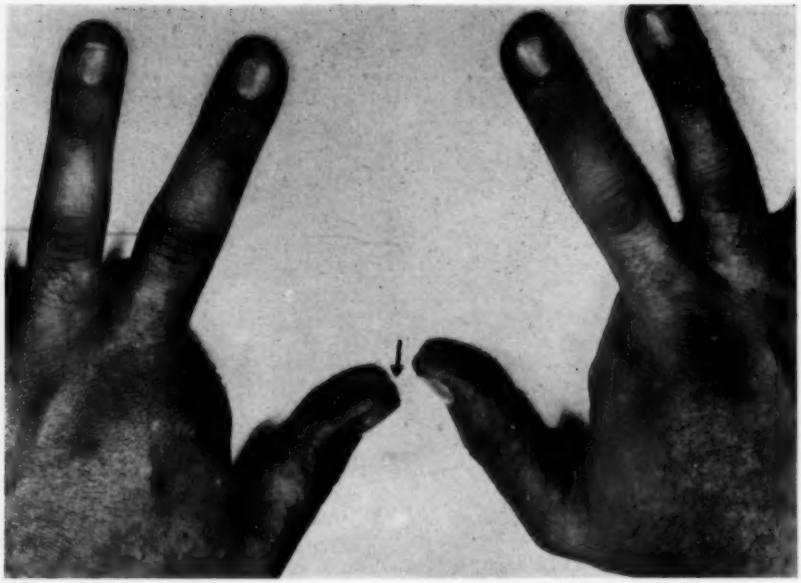

Fig. 9. The injury shown in Fig. 6 has caused amputation of both index fingers. Further, a new roentgen wound has arisen on the outer phalanx of the left thumb.

suitable set of regulations, which should be rigidly observed even when difficulties arise in surgical procedure.»

Too much stress cannot be laid on these words of warning, particularly in view of the fact that the injury described above is by no means unique, whether among physicians or dentists, even though the degree of severity of the injuries has, happily, but seldom been so pronounced as in the present case. It is necessary to emphasize strongly to the young medical students that they must carefully follow all directions with regard to protection against irradiation. They must be carefully informed of the chief features of the biological effects of irradiation and its cumulative action, with the risks this involves.

3. The third patient was a male laboratory assistant, born in 1927 (hospital record number 912/1947). Since 1945 he had worked at a metal-works, and for about 2 years he had assisted in roentgen screening of castings for the detection of any possible air pockets in the material. From the beginning of December 1946, the patient, in order to save time, had now and then stepped in front of the protective wall provided in connection with the fluorescent screen and with a short steel-rod, about 12 cm long, marked the point where air pockets may have occurred. On these occasions he wore

neither lead rubber gloves nor lead rubber apron. — The roentgen tube was generated by 140 kilovolts and 18 milliamperes and furnished with an extra filter corresponding to 0.01 mm Cu. The apparatus filter of the tube equalled approximately 1 mm Al. The distance from the tube to the screen was 1 m. For the purpose of the examination the castings were placed as close to the screen as possible. During the fluoroscopy the patient had kept 70—80 cm from the focus of the tube.

At the middle of January 1947 the patient began to be troubled by a swelling and discolouring of the right index finger. On the 20th of January 1947 he called on a doctor. Some time afterwards he noticed the first signs of a blister formation. This was treated conservatively. Gradually similar changes, though less pronounced, appeared also on the left index finger. The nail of the right index finger became loose and, at the beginning of February, it fell off. Only then the doctor was informed of the nature of his patient's work. The patient was immediately sent to a radiologist, who directed the patient to Radiumhemmet. He was admitted on the 11th of February 1947. The patient then displayed an ulcerous dermatitis on the distal third part of the right index finger which was without a nail (Fig. 6). The thumb of the same hand showed a circular blister formation on its outer tip, of an approximate diameter of 1.5 cm. Also on the left index finger an injury was visible on the top phalanx with epidermal desquamation and an ulceration, the diameter being, approximately, 1.2 cm. The skin on the tip of the thumb of the left hand revealed a firm, almost horny consistency with two chap formations. No epilation occurred on the back of the hands. A dry desquamating epidermitis was noticeable in an area corresponding to the metacarpophalangeal joints on the right hand. No blood changes suggesting irradiation injuries were to be found. First, the treatment was only conservative with fomentations and bandages with indifferent ointments. — At the beginning of March 1947, an epilation was observed within the right temporal region. Still, 3 or 4 months later the hair had again begun to grow (Figs. 7 and 8). — Since, after two months, the ugly wound on the right index finger failed to disclose any noteworthy tendency towards healing, an amputation of the right index finger, just proximally to the outer part of the interphalangeal joint, was performed on the 18th of April 1947. The left index finger healed with a moderate atrophy of the soft part. — However, the wound after the amputation refused to heal. For this reason, at the middle of July 1947, an exarticulation in the metacarpophalangeal joint was undertaken. After that the patient remained healed up to April 1948, when the left index finger became discoloured with a necrotic process and gangrene setting in on the outer phalanx. Also this finger was then amputated, at another hospital.

At the end of September 1948 the left thumb again began to cause trouble with pronounced soreness and chap formation (Fig. 9). — For the time being the patient has been advised to seek rest, while being treated conservatively, so far with satisfactory results.

Briefly put, a young man, who for 2 years has been occupied in fluoroscopy of castings, disregards, in order to hasten his work, such regulations as have been issued at his roentgen establishment, for the purpose of protection against irradiation. He pays for his rashness with the loss of his two index fingers. In addition, a new irradiation ulcus has recently appeared on the tip of the left thumb which, for the time being, incapacitates the patient for work.

These three patients have been selected with a view to illustrating different types of irradiation injuries. Our coworkers at the Radiophysical Institute, in the course of their inspection duties, have constantly

to record new cases of irradiation injuries of a varying degree of severity. Mostly blood changes are noticed and, not rarely, also dermal injuries. — In this connection mention should, perhaps, be made of the risk of mutations that are to be found. The work on this subject by MUELLER, the Nobel Prize winner, gives food for thought.

In Sweden, special directions have been published for every roentgen establishment and, on account of injuries that have been observed among various categories of personnel, the Radiophysical Institute has, in addition, issued a memorandum offering general advice and instructions. Such memoranda have been sent to all those in charge of any roentgen work. — The control has been intensified both with regard to the protective arrangements as such at the roentgen establishments and the steps taken to enforce observance among the staffs of the orders prescribed for the performance of their duties. — Still, experience shows that much systematic instruction will still be required before we can hope to overcome the negligence and lack of judgment that, unfortunately, are met with but too often in connection with roentgen and radium irradiation. To achieve this purpose, nothing less than a cooperation between all those who wish to see a better order prevail will suffice.

SUMMARY

More people than ever are nowadays engaged in work connected with radium and roentgen irradiation, in Sweden about one in every thousand of the population. It has, therefore, become a matter of urgency to emphasize the risks of irradiation injuries.

The author describes three cases representing different kinds of injuries. In view also of the fact that an increase in the number of irradition injuries has recently occurred in Sweden, the author has made it his purpose, in the present paper, to reinforce previous warnings of the dangers inherent in the use of roentgen rays and radium, stressing the importance of invariably observing every possible care in the work and strictly following prescribed protective measures.

ZUSAMMENFASSUNG

Heutzutage sind mehr Leute als je mit Arbeit beschäftigt, die mit Radium- und Röntgenstrahlung zu tun hat, in Schweden etwa ein Mensch auf tausend der Gesamtbevölkerung. Es ist deshalb nunmehr äusserst wichtig, die Gefahren der Bestrahlungsschädigungen zu betonen.

Verf. beschreibt drei Fälle, die verschiedene Arten von Schädigungen darstellen. U. a. angesichts des Umstandes, dass die Anzahl der Strahlenverletzten in letzter Zeit in Schweden zugenommen hat, bezweckt Verf.s vorliegende Arbeit, die früheren Warnungen vor den die Verwendung von Röntgenstrahlen und Radium begleitenden Gefahren einzuschärfen, unter Betonung der Bedeutung des ständigen Beachtens jeder möglichen Vorsicht bei der Arbeit und eines genauen Befolgens vorgeschriebener Schutzmassnahmen.

RÉSUMÉ

Le nombre de gens s'occupant de travaux où ils sont exposés à l'action du Radium et des Rayons Roentgen est aujourd'hui plus grand que jamais et représente, en Suède, environ un millième de la population. Aussi est-il devenu urgent d'insister sur les risques des lésions par irradiations.

L'auteur décrit trois cas représentant différent types de ces lésions. A cause, également, du fait que ces accidents dus aux irradiations ont augmenté en Suède ces derniers temps, l'auteur s'est proposé, dans ce travail, de donner plus de poids aux mises en garde antérieures contre les dangers de l'usage des Rayons Roentgen et du Radium, et il souligne combien il importe d'observer invariablement toutes les précautions possibles au cours du travail, en prenant strictement les mesures de protection prescrites.

FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT OF KAROLINSKA SJUKHUSET
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THE RADIOLOGICAL ASPECT OF THE UTRICULUS PROSTATICUS DURING URETHROCYSTOGRAPHY[1]

by

Nils P. G. Edling

When the para-mesonephric (muellerian) ducts atrophy in the male embryo the fused caudal ends remain as the prostatic utricle (vagina masculina or virilis). The utricle forms a blind pouch in the midplane of the prostate, directed backwards and upwards, from the opening on the collicle between the orifices of the ejaculatory ducts.

The size and shape of the utricle varies. According to the anatomists the length usually is 8—10 mm and the width near the opening 1—2 mm, increasing to 4—6 mm at the blind end. The wall of the utricle may contain glands, whose shape and function in no manner differ from the surrounding prostatic glands. Abscence of the utricle is very rare.

In the roentgen literature one finds that HOWARD (1948) has made an endoscopic and roentgen study of 14 unselected males with hypospadias for remnants of the caudal ends of the muellerian ducts. The degree of differentiation of the muellerian ducts and the severity of penile and other genital anomalies were closely related. HOWARD concludes that utricular enlargement in hypospadias represents an intersexual type of development rather than purely local isolated anomalies. PIERGROSSI (1948) has described one case of contrast filling of the utricle during urethrography. He demonstrates typical pictures of the case and suggests that the urethro-utricular reflux is caused by atony in the muscular coat of the utricle after chronic gonorrheal urethritis. According to PIERGROSSI this roentgenological finding is very rare.

According to the writer's experience the contrast filling of the utricle during urethroscystography appears to occur not infrequently. During 1948, in about 700 male patients urethrocystographed one or more times, 17 showed contrast filling of the utricle or its opening. The examinations

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were performed with water-soluble contrast mediums of abrodil-type, and the same substance was used during both injection and micturition.

The intention of this paper is to describe the clinical and roentgenological character of these 17 cases with utricular contrast filling.

Nine patients were in the third and fourth decade. Three patients were younger, five older. The youngest patient was 10 years old, the oldest 72.

One of the cases — a boy 12 years old, the only one suffering from incontinence — had been operated for hypospadias, and had a widening of the symphysis pubis of 2 cm. The prostatic urethra was very short and not fully contracted, that is, the sphincters were insufficient. In the remaining cases the urethra was contracted during injection. Four patients had nocturnal enuresis and one was a sexual neurotic psychopath. Six patients showed signs of prostatitis, and two signs of hypertrophy — in addition there was one case with signs of both prostatitis and hypertrophy verified by biopsy after electroresection. Finally, the two remaining cases suffered from hematuria of unknown origin.

That four cases with nocturnal enuresis should occur in this short series is rather remarkable. The relatively great number of patients with prostatitis is explained probably by the fact that inflammatory changes may cause rigidity of the utricular opening, predisposing an easy contrast filling.

The size and shape of the utricle varied in the different cases. The largest utricle measured 16 mm by 13 mm, the smallest one 4 mm and 1 mm on the films (allowing for magnification about 12 mm by 9 mm and 3 mm by 0.8 mm, respectively). Two cases showed a density in the opening of the utricle only, about the size of a pin's head. The lumen of the cavity was usually pear-shaped, the narrowest portion being at the opening (Figs. 1, 2, 3). In some cases the utricle communicated with the urethra by a duct. In two cases the shape was more spherical (Fig. 4). The contours were smooth with the exception of irregular outlines in one case.

In this series, the hypospadias case had one of the smallest utricles and no rudimentary vagina could be demonstrated. The four patients with nocturnal enuresis and the patient with the sexual neurosis had small utricles also. The larger of the spherically shaped utricles, the largest in the series, belonged to one of the hypertrophy cases. Probably, the dilatation was due to a valvular stenosis at the opening. The patient with the irregular utricle had a post-gonorrheal stricture and prostatitis, and probably there were post-inflammatory changes in the utricle, too. In the remaining cases the utricle had normal shape and smooth contours.

The micturition examination succeeded in 15 of the 17 cases. In one of these visualization of the utricle appeared only during micturition, while

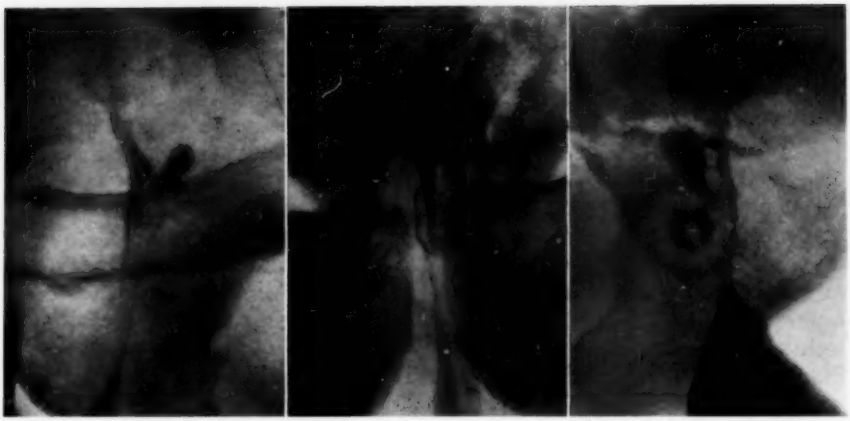

Fig. 1. Fig. 2. Fig. 3.

Figs. 1, 2, 3. Utricular contrast filling of three different cases in right oblique view, frontal view, and left oblique view, respectively. Prostatic urethra normally contracted. In the first figure the utricle partly overlaps a calculus in the prostate.

in 2 cases it was more complete during micturition than during injection. In the remaining cases it was more evident, or demonstrable only, during injection. The dilatability of the prostatic urethra was normal or, in spite of hypertrophy, good. Thus, as in most other changes recognized during urethrocystography, the micturition examination afforded additional information to that obtained from the injection examination.

In 29 normal cases — urethrocystographed earlier by the writer — none showed a utricular contrast filling. These findings are in good agreement with the fact that in all normal cases no other para-urethral organs, such as bulbo-urethral and prostatic glands, were demonstrable. These studies seem to indicate that ducts of the para-urethral organs opening into the urethra possess a type of closing mechanism which is quite competent under normal conditions. The cause of the contrast filling in the present series seemed to be either a functional disturbance, or a post-inflammatory change with rigidity of the utricular opening.

It is possible that, in cases of prostatitis, the utricle may be so deformed and dislocated by shrinkage that a contrast filling cannot be recognized as such. It may perhaps be indistinguishable from a prostatic duct or gland, changed into a pathological cavity by the inflammatory process. Therefore in such cases, a utricular contrast filling may be present, and yet one cannot diagnose it in the urethrocystogram.

Fig. 4.

Fig. 5.

Fig. 4. Widened cyst-like utricle in a case of hypertrophy. Right oblique view.

Fig. 5. Contrast filling of the utricle and of cavities in the right portion of the prostate. The utricle has a slightly irregular shape and has a more vertical course than usual, just behind the urethral lumen. Left oblique view.

The presence of a contrast filling of the utricle in urethrocystography usually does not seem to be of special diagnostic importance. However, from the differential diagnostic point of view, with regard to cavities in the prostatic glands after inflammation, it is necessary to recognize the possibility of contrast filling of the utricle (Fig. 5).

SUMMARY

The writer has studied 17 cases of contrast filling of the prostatic utricle during urethrocystography. The cause of the visualization seemed to be functional disturbance, or post-inflammatory changes. The finding has its main importance from the differential diagnostic point of view, with regard to post-inflammatory prostatic cavities.

ZUSAMMENFASSUNG

Verf. hat 17 Fälle von Kontrastfüllung des Utriculus prostaticus bei Urethrozystographie studiert. Die Ursachen des Sichtbarwerdens schienen funktionelle Störungen oder Veränderungen nach Entzündungen zu sein. Der Befund ist vor allem in differentialdiagnostischer Hinsicht bedeutungsvoll im Hinblick auf Höhlenbildungen der Prostata nach Entzündungen.

RÉSUMÉ

L'auteur a étudié 17 cas de remplissage de l'utricule prostatique au cours de l'uréthrocystographie. La cause de cette apparition sur les clichés semblait devoir être recherchée dans un trouble fonctionnel ou dans des altérations post-inflammatoires. Les observations sont surtout importantes pour le diagnostic différentiel vis-à-vis des cavités prostatiques succédant à une inflammation.

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FROM THE GENERAL DEPARTMENT OF RADIUMHEMMET (CHIEF: PROF. ELIS BERVEN), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN.

MALIGNANT MELANOMA OF THE SKIN[1]

Report of 341 Cases treated during the Years 1929—1943

by

Bengt Sylvén

This paper will summarize the results of treatment obtained at the Radiumhemmet in cooperation with several Swedish surgical departments in patients with cutaneous malignant melanoma, admitted during a 15-year period from 1929 through 1943. Our results are gained by means of conservative surgery in combination with irradiation. This analysis was performed with a view to elucidating factors of importance and possible deficiencies in present principles of treatment in order to improve future methods. For this reason, data regarding the indications for palliative treatment by surgery and radiation as well as records of many peculiar cases have been omitted. Detailed clinical reviews by MIESCHER (45), MOIR *et al.* (47), PACK & LIVINGSTON, and others (1, 3, 4, 9, 34) cover all pertinent aspects. The report was limited to melanomas of the skin in order to avoid cases with regional gland stations inaccessible to clinical classification. The tables are for comparison kept close to those published by PACK, PERZIK & SCHARNAGEL (54), who reviewed 862 cases seen at the Memorial Hospital from 1917 to 1946. For previous reports from Radiumhemmet the readers are referred to a paper by SCHARNAGEL (61) on cutaneous melanomas treated between 1921 and 1930, and further the epibulbar melanomas have been dealt with by LARSSON (39).

Considering pathological and biological aspects, the heterogeneity of this group of tumours is regarded as an established fact (5, 16, 52). Present insufficiencies in histological diagnosis and classification also influence the clinical management of melanomas to a certain degree. All the same, the factors for proper treatment are defined by the pronounced tendency to early and wide-spread dissemination and by the high degree of radio-

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resistance, generally displayed by malignant melanomas. This will rule out clinical experimentation in early cases. Rational treatment must therefore be based on the eradication of the primary melanoma and its satellites without undue delay. It should further be recalled, that our very limited possibilities to determine the true extent of the disease necessitate more radical and wider excisions than are usually performed. More patients will evidently be salvaged by too wide excisions than by inadequate or repeated operations. We hope that in suitable cases excision and dissection »in continuity» for melanoma, as advocated by the Memorial Hospital Group (52—56), and further the »prophylactic» dissection of regional glands (1, 9, 25, 28, 33, 34, 45, 52—54, 66) will provide more cures than previously used methods have given.

Irradiation treatment by means of large or »hypermassive» dosage may give cures in selected early cases of primary melanoma (11, 12, 23, 24, 29, 38, 42, 43, 47, 51). However, this method involves considerable delay in time and heavy tissue and vascular reactions, which may favour tumour spread. For these and other reasons we consider it unjustified to take the responsibility for routine irradiation of primary melanomas in early stages, in particular when safer methods are available (cfr. 58). In advanced cases, irradiation treatment is on the other hand of palliative value, which will be mentioned below.

Calculation of End Results and Classifications

Our series comprises a total of 341 cases during the 15-year period mentioned above. Treatment was refused in 50 cases due to advanced metastases and/or senility. The remaining 291 verified cases available for analysis were divided into one »indeterminate group» and another »determinate group» according to recent suggestions by MacDonald (41). All living patients' records were brought up to December 1948 by means of our follow-up system.

In order to facilitate comparison with other statistics the conventional clinical 5-year cure rates are stated in the main tabulation of results (Table IV). This results in cases developing metastases after a 5-year period of apparent health (»latent» metastases or »delayed metastatic growth») being reported as cured. Since the percentage of such latent metastases was found to be fairly large, a simultaneous report of what is called »end results up to 1948» is made. The latter figures are more correct from a biological point of view and will come closer to the actual course of malignant melanoma.

Due to high average age of our patients a fairly high incidence of intercurrent deaths was met with. A survey according to the principles of MacDonald will consequently entail a lower net five-year end result

than would actually be the case if corrections were made for such intercurrent deaths. In these particular cases, however, the reviewer has not been able to determine the cause of death in every patient under question, nor was it possible to exclude that patients had tumour remnants or silent metastases, and therefore it seemed unjustified to present corrected figures.

All patients have been classified in stages according to the extent of the tumour process at admission, as ascertained by clinical means including all available radiographic and laboratory methods. This clinical screening is naturally impaired by similar errors as are all others of the same type; unavoidable mistakes with reference to lymph node screening and blood-borne metastases are apparent. The original classification was kept without later reclassifications.

Stage I. Localized melanoma confined to the skin. Local recurrences and near-by deposits in cutaneous lymphatics are included.

Stage II. Cases with regional lymph node metastases confined to one gland station only.

Stage III. Metastatic involvement of two or more groups of glands, and cases with distant metastases evidencing generalized tumour process.

Histo-pathological reports of primary tumours and all operated metastases were available. Nevi with questionable malignancy are not included unless they have developed metastases later on. Tumours of doubtful nevogenic origin were discarded. Previous classifications in »melanocarcinoma» and »melanosarcoma» were impossible to maintain, and therefore we resort to the common term »malignant melanoma» until more correct distinctions can be made (cfr. ALLEN).

Incidence of Melanoma

Relative frequency. — During this 15-year period a total number of 4,867 patients with skin epitheliomas applied for treatment at Radiumhemmet. The ratio of malignant melanoma to skin carcinoma was thus 7 : 100. This ratio was considerably higher in young age groups than in older ones. Detailed analysis with regard to age groups and patients' occupation was omitted (cfr. 59).

Distribution. — The regional distribution of malignant melanoma in this series is recorded in Table I, which shows the previously well known differences in distribution from that of skin epithelioma. The possible etiological significance of this fact has been repeatedly discussed (59) but no clear explanation has been reached. The distribution of malignant melanoma is also different from that of common pigmented nevi (5, 54).

Sex. — In this series 57 per cent were females and 43 per cent males. Females were in majority in most age groups (Table VII).

Age. — The age distribution chart (Fig. 1) reveals the highest incidence 37 and 43 per cent in the age groups between 40 to 90 years. The youngest patient was 17 months

at admission, and the oldest 91 years. The ratio of patients admitted to treatment and those not admitted is shown in Fig. 1.

Table I

Distribution of 341 Cases of Malignant Melanoma according to Site of Lesion

Site	Per cent	
Lower Extremity		31.0
Exclusive of feet	14.3	
Feet, exclusive of nails	16.1	
Ungual	0.6	
Head and Neck		33.6
Trunk		26.3
Upper Extremity		8.4
Exclusive of hands	4.1	
Hands, exclusive of nails	2.6	
Ungual	1.7	
Scrotal		0.3
Unknown primary site		0.3

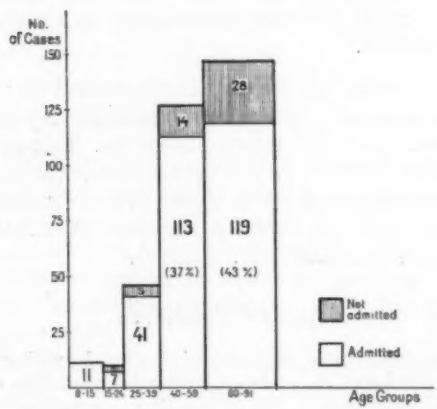

Fig. 1. Distribution of age groups in 341 patients with malignant melanoma of the skin.

The Precursory Lesions

Of malignant melanomas of skin 40 to 65 per cent are commonly stated to originate in congenital or acquired pre-existing nevi. In elderly persons a small number of melanomas further arise in so-called »precancerous melanosis» (Lentigo maligna). The following data are of no value as far as the histogenesis of malignant melanoma is concerned (cfr. 5), and will only be mentioned for the purpose of the records.

Table II

Percentage of Precursory Lesions in Malignant Melanoma of Skin

Colour of Primary Melanoma	Incidence of Pre-existing Congenital Nevus		
	Feet	Hands	All other Sites
Black	0 %	0 %	40 %
Brown	50	50	50
Blue or purple	0	0	50
Red, pink or skin-coloured	11 %	22 %	23 %

Pre-existing pigmented nevi. — With reference to the different colours and degrees of pigmentation in the present series of melanoma, a significant disparity was found in the incidence of previous »congenital» nevi, or nevi appearing during infancy. Patients with pigmented melanomas (black, brown, and blue or purple) related a history of a previous pigmented nevus since childhood in 40 to 50 per cent of all cases, except those of hands and feet (Table II). On the contrary a previous pigmented mole was only recorded in 23 per cent of patients with non-pigmented melanomas. Almost all melanomas (except part of the brown ones) appearing in hands and feet seem thus to be acquired (Table II). Our series further include one case of malignant melanoma arising in »bathing-trunk» nevi (Fig. 2).

These figures suggest that the innocent pigmented moles (intradermal nevi) can only be considered as precursors to part of the malignant melanomas. The majority seem to be acquired, and probably arise from epidermal cells (cfr. 5). This lends further emphasis to the possible rôle of extrinsic factors for the initiation of melanoma (36).

Precancerous melanosis. — The records include 13 cases (4.4 per cent) of melanoma preceded *in loco* by a

Fig. 2. Woman, aged 21, with multicentric rapidly growing giant melanomas in previous bathing-trunk nevus. At admission, 4 months after first sign of malignant change, the tumour process was generalized. (Case record No. 7001/1936.)

Fig. 3. Fig. 4.

Fig. 3. So-called »precancerous melanosis» with a richly pigmented melanoma at center. (Case record No. 9710/1940.)

Fig. 4. Following radical excision and plastic repair, this patient was living and well for 7 years.

typical precancerous melanosis with progressive growth (21, 44, 15). Most of these were located in the face. The induction time from the appearance of melanosis until established melanoma varied between 3 to 42 years (average induction time 11 years). Multiple foci of melanoma were repeatedly observed. The average age of these patients at admission was 70 years.

Mode of Growth and Pigmentation

With regard to gross anatomy and mode of growth two main types of cutaneous melanomas may be distinguished. In most cases (97 per cent) small primary tumours showed marked tendency to infiltrative growth and early dissemination. The second type, characterized by large exophytic tumours with a chiefly expansive mode of growth and a more benign course, was registered in about 3 per cent of our cases.

A reversed ratio of similar melanoma types is found in animals. The more benign type has previously been recognized in a number of animals, such as horses (31, 62), dogs (7, 50), cats (45), mice (14, 30, 35, 65), and cattle (6), while the first mentioned infiltratively growing type occurs more seldom. Only a few verified melanomas have been obtained under long-continued applications of carcinogenic hydrocarbons to the skin of experimental animals. Passey (57) reported three exophytic melanomas in dogs; one was malignant. Following the application of benzpyrene Schürch (63) found one in-

Fig. 5. Fig. 6. Fig. 7.

Fig. 5. Exophytic, mainly expansively growing, grape-like malignant melanoma in a man, aged 77. (Case record No. 5710/1934.)

Fig. 6. Patient's condition 10 days after a wide diathermy block dissection with subsequent superficial coagulation. Removed skin area 4 × 5 cm.

Fig. 7. Two months later, the wound was healed without grafting. Patient died 8 years later free from tumour.

filtrating and metastasizing melanoma in a rabbit. The commonly propagated laboratory melanomas of HARDING-PASSEY and CLOUDMAN differ in several respects from the behaviour of human malignant types (cfr. 5).

For the purpose of the records some attention was devoted to the capacity of pigment formation in primary melanomas, as evidenced by the colour of the primary tumours. The following percentage distribution was found in our determinate series of 251 patients:

Black	25	per cent
Brown	28	» »
Blue or Purple	13	» »
Red, Pink or Skin-coloured	34	» »

The ratio of melanomas poor in melanin is probably larger in this series than in previous ones (47). In untreated patients the red or skin-coloured melanomas were found to run a more rapid course than the pigmented ones (Table XIII).

Routes of Dissemination

Part of this series was suitable for study of the relative frequency of the different modes of dissemination from the primary tumours (Table III), and thus some common clinical types may be distinguished (cfr. 52). The majority (54 per cent) developed early lymph node metastases diagnosed previous to or shortly after the treatment of the primary tumour. Latent gland metastases were registered in 7.5 per cent. Early generalization via the blood stream was further diagnosed in 28.5 per cent. This occurred either without simultaneous regional gland involvement (11.5 per cent) or with such involvement (17 per cent). Finally, a small number of cases (7.5 per cent) grew for years in the superficial lymphatics surrounding the primary locus (cfr. PACK & LIVINGSTON, p. 2078—2079).

Cases with early hematogenous spread from the primary focus constitute more than one fourth of our patients, which means that these were most likely already beyond help at admission to the hospital or shortly afterwards.

Regarding cases with regional lymph node involvement particular attention was focused on the possible time during which the tumour process was confined to the nodes. This is a question of great importance for the management of Stage I and II cases, and the figures to be presented show unfortunately that the lymph node barrier is broken very rapidly.

Table III

Routes of Dissemination in 197 Cases of Malignant Melanoma of Skin

Apparent Expansive Growth		2.5 %
Mainly Infiltrative Growth		97.5 %
Local lymphatic spread during several years, followed by fatal metastases	7.5 %	
Early metastases to regional lymph nodes	54 %	
Simultaneous lymph node metastases and hematogenous generalization	17 %	
Early hematogenous spread without previous or simultaneous metastases to regional lymph glands	11.5 %	
Late lymph node metastases and/or other »delayed metastatic growth»	[1] 7.5 %	

[1] Metastases became evident after 5 to 16 years period of apparent health.

Melanoma cells are probably set free and carried by the blood a long time before clinical signs of distant metastases become evident. Previous authors have demonstrated tumour emboli in bone marrow punctures several months before the diagnosis of generalization was possible (17—20). This method may in future provide a more correct and earlier staging of melanoma patients, and further make mutilating operations unnecessary, as was discussed by DUBOIS-FERRIÈRE.

Fig. 8.

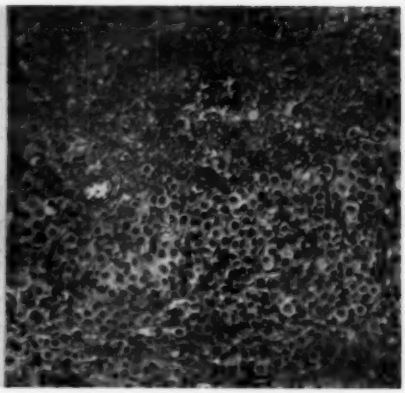

Fig. 9.

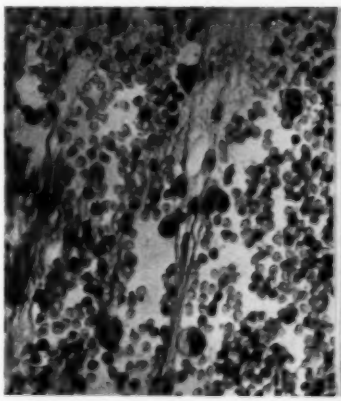

Fig. 10.

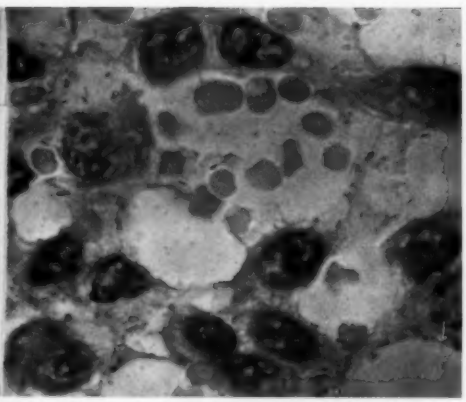

Fig. 11.

Fig. 8. The following slides show wide-spread involvement of blood vessels and lymphatic permeation in a case of recurrent non-pigmented melanoma of the calf. A medium sized superficial vein is invaded by tumour cells, growing into a central thrombus. (Case record No. 6904/1934.)

Fig. 9. Melanoma cells invading blood clot and freely capable to produce innumerable tumour cell emboli. (Slide No. 250/1936.)

Fig. 10. In a small subcutaneous focus isolated cells were found to grow among the blood corpuscles in a ruptured vessel.

Fig. 11. In such foci the tumour cells show pronounced loss of cohesion, which favours embolic spread, and illustrates the urgency of wide removal without undue delay (cfr. text).

Differential Diagnosis

Regarding the importance of early clinical diagnosis it should be mentioned that in most pigmented melanomas (black, brown, blue, and purple) a correct diagnosis was made at the patients' first visit to the local physician. This was unfortunately not the case in patients with non-pigmented tumours (red, pink, or skin-coloured). The following examples will illustrate actual misinterpretations made by our staff.

Two brown melanomas were mistaken for pigment-forming squamous carcinoma and a senile wart, respectively, and were treated by radium implantation. One blue melanoma was taken for an angioma and electrocoagulated.

Eight cases with non-pigmented melanoma in the face were treated under the following provisional diagnoses: basal-cell carcinoma (3), squamous carcinoma (3), and angioma (2). Two melanomas located on the trunk got a first diagnosis of basal-cell carcinoma and angioma, respectively.

Fig. 12.

Fig. 13.

Fig. 12. This non-pigmented malignant melanoma was for one year interpreted as a plantar corn. Amputation was refused; the woman died of metastases 6 years after first symptom of tumour. (Case record No. 6954/1934.)

Fig. 13. In 1939 a woman aged 45, developed a small spot on her finger. This was mistreated by caustics and inadequate surgery. She entered this hospital in September 1941 with recurrence 15 × 18 mm in size, node metastases and pulmonar involvement. The primary was treated for palliative purposes with Roentgen irradiation (4,400 r in 8 days; 195 kV) without apparent effect. Length of survival from first symptom to death 30 months. (Case record No. 10947/1941.)

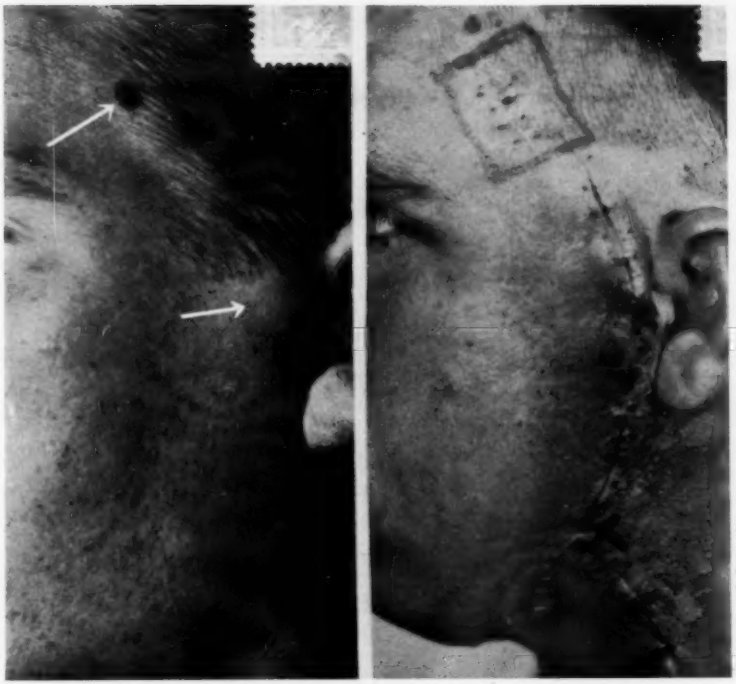

Fig. 14. Fig. 15.

Fig. 14. Previous to admission, a young man had a black nevus for 18 months, which was treated by incomplete electrodesiccation. This was followed by the development of preauricular and deep cervical nodes 9 months before admission. (Case record No. 6954/1934.)

Fig. 15. The nodes did not respond to preoperatively administered Roentgen irradiation (1,600 r). A radical extirpation and complete block dissection of cervical nodes was performed. Three months later distant metastases evidenced that generalization had actually occurred previous to operation. Length of survival from first sign of nevus to death 26 months, from the time of gland dissection only 8 months.

The non-pigmented melanomas on the feet and toes presented the greatest diagnostic difficulties; out of eight cases, 3 were misinterpreted as common plantar corns (Fig. 12), 1 was called a teleangiectatic granuloma, 1 a non-specific ulcer, another a diabetic gangrene, a seventh a chronic eczema, and the eighth a hemangioma.

Great harm was done by doctors, chiropodists, and beauticians, who treated early cases of malignant melanoma by freezing, caustics, and electric needling, whereby diagnosis and adequate therapy were delayed (Fig. 13—15).

Principles of Treatment Applied in this Material

Due to a variety of circumstances beyond our control uniform therapy methods have neither been possible to apply in Stage I nor in Stage II patients (cfr. 61). In general it may be said, that the primary tumours have at this or other hospitals been subjected to local interventions either by clean surgery, or by electrosurgery. Depending upon the site of lesion, more or less wide block excisions were made which is considered as »restrictive» or conservative surgery (Fig. 3 & 4). Large excisions and/or mutilating operations were performed only in cases with recurrences or local secondary growths.

Diathermy block excisions included removal of the primary tumour, the surrounding skin area, all of the underlying fat tissue, and preferably also the deep fascial covering. Afterwards the wound was superficially coagulated with the diathermy current, and then left to granulate. In about 2—4 months the defect was replaced by soft scar tissue. In a few cases secondary skin-grafting was done. The results are illustrated in Fig. 6 & 7.

Patients with suspected or manifest lymph node involvement have caused considerable difficulty. Prophylactic gland dissection advocated by a number of previous authors has not been used. In Stage I cases with questionable regional nodes irradiation therapy in moderate dosage (1,400—2,000 r) was administered, and then the glands were closely watched. If the examination later on (Table X: after 1 to 19 months) indicated metastatic growth, dissection was performed. Patients admitted in Stage II were either operated at once and then subjected to postoperative irradiation (Roentgen or teleradium), or otherwise preoperative irradiation (1,600—2,800 r) was first given in order to facilitate the subsequent gland dissection (Fig. 14 & 15) in cases with debatable operability. Stage III patients were naturally referred to palliative treatment only, preferably by Roentgen irradiation. For additional treatment data the readers are referred to previous report (61).

The plans of treatment just outlined indicate that the primary melanomas were in general treated as surgical emergencies as early as 20 to 30 years ago. The regional gland deposits were, however, treated more or less like all other cancer metastases without realizing what delay in time could effect.

Report and Evaluation of Results

High percentage cure rates were obtained in this material (Table IV) as compared with previous reports from other clinics (1, 3, 4, 9, 10, 13, 28, 37, 47, 54, 60); the conventional 5-year cure rate amounts to more than 34.6 per cent (uncorrected), and the late end result up to 1948 is 30.8 per cent (uncorrected). The over-all 5-year survival rate was 9.7

Table IV

Tabulation of Main Results[1]

Total number of patients applied for treatment	341
Total number of patients admitted	291
Indeterminate group	
Dead within five years of other causes, probably without recurrence of melanoma	28
Lost track of	0
Total number of indeterminate results	28
Determinate group	
Total number	263

	Conventional 5-year cure rates	End results at 1948
Failures		
Dead as a result of melanoma	163	167
Living with recurrent melanoma	9	15
Total number of failures in treatment	172	182
Successful results		
Free from melanoma	91	81
Prepubertal group, all living	11	11
Adult group, living free from melanoma	60	50
Adult group, dead of other causes but free of symptoms more than five years after treatment	20	20
Conventional net five-year end result	34.6 per cent	
End result at 1948		30.8 per cent
Over-all end result at 1948 including all patients		23.7 per cent

[1] Form according to Dr. ELEANOR J. MACDONALD.

per cent in the Memorial Hospital series of 595 cases (54), and is more than 26.7 per cent in ours. The analysis to be presented indicates (Table V & VI), that this high cure rate is due to the high percentage distribution of Stage I patients in our series. Our cure rate in Stage II patients (Table VI: 8.0 and 6.7 per cent) is on the same low level as that obtained in most other clinics.

This illustrates the inadequacy of reports only including end-results (41). For proper evaluation of methods and results, clinical staging is of prime importance. With reference to this particular material, we happen to know that the Memorial Hospital series include a larger percentage of advanced cases than our material does (54; and personal communication), and this renders the results incomparable.

It is further evident from Table VII, that the *prepubertal* (juvenile) *melanomas* do not behave like other malignant melanomas although their histology is indistinguishable from those occurring in later age groups.

Table V

Distribution of Clinical Stages at Admission

	No. of patients	Percentage
Stage I	188	55
Stage II	77	23
Stage III[1]	76	22

[1] Including 50 patients not admitted.

Table VI

Cure Rates in Relation to Stage at Admission

Only adult patients of Determinate Group are included.

	Total No. of treated Patients	Conventional 5-Year Cure Rates in per cent	End Results in per cent up to 1948
Stage I	151	48.3	43.0
Stage II	75	8.0	6.7
Stage III	26	3.8	0

Table VII

End Results at 1948 in 263 Cases of Melanoma in Relation to Age Groups

Age Period and Sex	Total No. of Cases	No. of Cured Cases	End Results in per cent at 1948
Prepuberty	11	11	100
Puberty through 24 years:			
Females	3	1	33
Males	4	3	75
25 through 39 years:			
Females	26	9	34
Males	15	4	27
40 through 59 years:			
Females	65	14	21
Males	45	10	22
60 years and over:			
Females	52	17	33
Males	42	12	28

This corroborates previous statements (1, 5, 52, 54—56, 64) and calls for separation of the prepubertal melanomas so far clinical reports are concerned. A few actually metastasizing melanomas in children have been reported (49, 64).

Table VIII

End Results at 1948 in 252 Cases of Malignant Melanoma of Skin in Relation to Primary Site of Tumour and Stage at Admission

Prepubertal melanomas not included.

	Stage	Total No. of Cases	No. of Cured Cases	Cure Rates in per cent at 1948
Lower extremity:				
Leg, exclusive of feet	I	21	8	38
	II	11	1	9
	III	3	0	—
Feet, exclusive of nails	I	22	7	32
	II	11	0	—
	III	6	0	—
Subungual	I	2	0	—
Head and *Neck*	I	56	32	57
	II	23	0	—
	III	3	0	—
Trunk	I	34	10	29
	II	24	3	12
	III	11	0	—
Upper extremity:				
Arm, exclusive of hands	I	7	3	42
	II	4	1	25
	III	2	0	—
Hands, exclusive of nails	I	9	4	44
	II	0	0	—
	III	1	0	—
Subungual	I	0	0	—
	II	2	0	—

No significant differences in cure rates can be claimed with reference to the various adult age groups (Table VII), nor are there any sex differences. The end results at 1948 in relation to primary site of melanoma are listed in Table VIII. In Stage I cases, a better prognosis was found for those involving the face and upper extremity (cfr. 1). A very poor prognosis indeed was obtained for most Stage II patients irrespective of site of primary lesion (Table VIII).

Before going into details it should thus be emphasized that the extent of the disease is above all the determining factor for the prognosis, and that our results are fair in Stage I patients, but poor in Stage II cases. This indicates that the methods so far applied by us until 1943 in the treatment of lymph node involvement are unsatisfactory.

Analysis of Stage I patients. — Only Stage I patients were suitable for evaluation of different methods used in the local eradication of pri-

Table IX

Results of Treatment of Primary Tumour and Local Recurrences in 151 Stage I Patients

	Total No. of Cases	No. and Percentage of Patients living free of Symptoms at 1948	No. and Percentage of postop. Local Recurrences	No. and Percentage of Lymph Node Metastases appearing after Operation	Hematogenous Spread shortly after Operation
Surgical excisions	88	40 (45 %)	16 (18 %)	37 (42 %)	10 (11 %)
Electro-surgery acc. to Radiumhemmet's practice	53	21 (40 %)	13 (24 %)	26 (49 %)	8 (15 %)
Irradiation followed by radical surgery	10	4 (40 %)	2 (20 %)	4 (40 %)	2 (20 %)

mary melanomas. As was mentioned previously, surgical and electrosurgical methods applied in our cases are regarded as conservative measures, which do not involve very wide excisions. The figures in Table IX indicate that similar results were obtained with both methods. The percentage of local recurrences was about the same after diathermy excisions, as performed at Radiumhemmet, than after clean surgery performed in this hospital or by other surgeons elsewhere. Neither was a significant difference found in the incidence of lymph node metastases following either method. The figures presented here cannot be said to favour any method *provided radical interventions are performed.*

Our series of local recurrences following non-radical operations is very variable as regards site of lesion, length of time between the first and second operations, appearance of metastases etc. It is therefore difficult to give a fair evaluation of the decrease in cure rate ascribable to the presence of local tumour remnants *per se.* It can only be stated that the cure rate is considerably diminished (cfr. 1). In Table IX a small number of cases is included, which were first treated by irradiation on an erroneous primary diagnosis, and then excised. The figures are given for comparison, and cures are ascribed to the subsequent surgical intervention.

A second point of extreme importance is the management of regional lymph node metastases appearing in Stage I patients after treatment of the primary melanomas. We would expect this group to show a better prognosis than those admitted to the hospital already in Stage II, and generally being in a more advanced state. Separate records were therefore prepared, and the first mentioned group is found in Table X. The final results are indeed very poor; only 5 patients are considered cured out of the whole number of 52 patients, or out of the 38 actually dissected patients (13 per cent). The figures in Table X suggest that our so-called »prophylactic» gland irradiation in its present form, as well as preopera-

Table X

Results of Treatment in 52 Stage I Patients who Developed Regional Lymph Node Metastases after Admission

	Total No. of Cases	No. and Percentage of Cures up to 1948	No. of Performed Gland Dissections	No. of Cases not operated	Delay in months between suspicion of metastases and time of operation (approx.)
Gland metastases following »prophylactic irradiation»; actual treatment direct surgery ...	26	1 (3.8 %)	16	10	1 to 19
Operated cases only		1 (6.2 %)			
Preoperative irradiation + subsequent gland dissection.....	12	1 (8.3 %)	12	0	1 to 7
Gland dissection + subsequent postoperative irradiation	10	3 (30 %)	10	0	1 to 4
Only Roentgen or teleradium irradiation	4	0	0	—	—

tively administered irradiation to such early node metastases is of questionable value. One of the main reasons for this seems to be that *both methods involve loss of time*, which means delay before gland dissections are performed (cfr. Table X). In any case, the cures obtained have to be ascribed to surgical intervention. Although the patients under question are not strictly comparable and in spite of the limited number of patients in different treatment groups, Table X indicates that more cures would probably be obtained when early gland dissection is performed. It is further a matter of argument if and when postoperative irradiation treatment to the gland regions should be given. This cannot be discussed with reference to the present material.

In a clinical material like this, it seems indeed impossible to evaluate so-called »prophylactic» gland irradiation with moderate or small doses. Following the radical excision of the primary melanoma, about one third of our Stage I patients will develop palpable nodes. This means that tumour cells must have reached the glands and remained undiagnosed since the time of the first operation. We know in this particular case, that irradiation treatment in its present state cannot kill melanoma cells deposited in lymph nodes, only a temporary suppression of growth can be effected depending upon the dosage given. From a scientific point of view, *this* type of »prophylactic» irradiation seems to be based on hypothetic considerations of questionable value. This and related problems were discussed more in detail by FORSSELL (27), EBENIUS (22) and others.

The final outcome in 151 Stage I cases is evidenced in Table XI. Out of 65 patients free of symptoms in 1948, 60 never developed any nodes. In the group with metastases to lymph nodes, only 5 were salvaged by the

Table XI

Summary of Events in Our Stage I Patients (Determinate Group) up to 1948

Living free of symptoms at 1948: 5—19 years after treatment of primary melanoma		65
Never got lymph node or other metastases	60	
Got gland metastases operated	5	
Living with recurrences and/or metastases		13
Dead as a result of melanoma		73
Lymph node metastases and subsequent hematogenous spread	47	
Insidious hematogenous spread from primary or unknown focus	21	
Simultaneous lymph node metastases and hematogenous spread	5	
Total number of patients		151

Table XII

End Results in Lymph Node Metastases Appearing in Stage II Patients

	Total No. of Cases	Living free of symptoms at 1948	Living at 1948 with rec. and/or metastases	Dead from melanoma	Duration in months of palpable nodes before dissection (average)	Time from dissection until generalization in months (average)	No. of recurrences in scar and/or new metastases (incomplete dissections)	Average age of patients[1]
Surgery, alone, no irradiation	3	—	—	3	1.6	4	—	55
Gland dissection + postoperative irradiation	25	1	—	24	3	12	14	55
Preoperative roentgen + subsequent gland dissect.	14	1	1	12	3	11	6	47
Preoperative teleradium + subsequent gland dissect.	11	3	—	8	3	10	3	52
Radiation alone, no surgery	[2] 22	—	—	22	—	[3] 8	—	54
	75	5	1	69	—	—	—	—

[1] Youngest patient 20 years, oldest 81 years.

[2] The nodes were in 21 patients most likely operable before irradiation was instituted, but 2 months later they were considered inoperable.

[3] Time from irradiation until generalization was evident. Patients in this group survived after irradiation from 4 months to maximum 4 years, average 15.6 months.

present treatment methods. Those who got insidious hematogenous spread (21 cases) could only have been salvaged by earlier diagnosis and treatment.

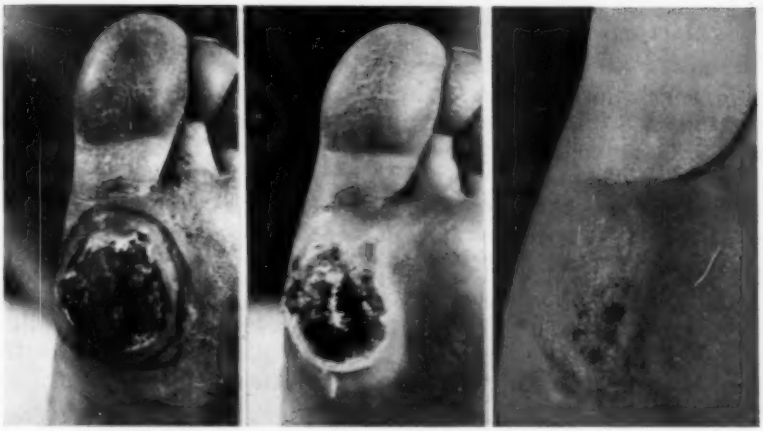

Fig. 16. Fig. 17. Fig. 18.

Fig. 16. At admission of a plantar malignant melanoma Stage I, the tumour was found to be non-pigmented with a papillomatous surface and measured $32 \times 35 \times 10$ mm. To a field 6×7 cm. in size we administered during 20 days a Roentgen dose of 4,700 r (100 to 180 kV). (Case record No. 6495/1934.)

Fig. 17. The melanoma had diminished considerably in size after 4 weeks.

Fig. 18. Two months after treatment, the ulcer was almost healed and no clinical signs of tumour were left. However, tumour remnants were verified by biopsy at this time, and later on in specimen obtained after amputation performed 4 months after radiation treatment. This case ran a fatal course 2 years after admission. Adequate surgery was delayed by irradiation.

Analysis of Stage II patients. — The variable structure of this group of cases warrants no detailed analysis regarding different treatment methods. Moreover, no representative number of patients only treated by surgery is included (Table XII) and consequently similar comparison as reported in Stage I patients cannot be made. Due to the fact, that many patients admitted in Stage II were in an advanced state, only part of the cases were operated upon (53 dissections in 75 patients). The more advanced gland involvement in Stage II excludes direct comparison and joint calculations with the early cases in Table X. It seems thus only justified to report, that the actual cure rate up to 1948 was 6.7 per cent (5 patients out of 75). The corresponding figure calculated on operated (selected) patients only was 9.4 per cent (5 patients out of 53). All cures are ascribable to surgical interventions.

For the purpose of the records, a comparison between early (Table X) and more advanced (Table XII) gland cases treated by dissection and subsequent postoperative irradiation may be made. In the early cases of gland involvement the cure rate was about

30 per cent, but fell down to 4 per cent when the more advanced, but still operable, cases in Table XII were considered. The latter figure is from a statistical point of view more correct than the former.

The considerations just mentioned illustrate the insufficiency in present plans for gland treatment, and indicate moreover that the lymph node barrier is in general broken through more rapidly than we have ever believed. This means that time is a very important factor for the successful management of malignant melanoma (cfr. 1), and loss of time should be avoided, here as well as in all other rapidly invading and early disseminating tumours.

Analysis of Stage III patients. — From the view point of curability these patients afford little interest and have to be referred to palliative measures. Untreated cases are, on the other hand, of interest for study of the length of survival, whereby the variable malignancy of melanoma will be illustrated.

Length of Survival in Fatal Cases

Study of fatal cases (Table XIII) reveals that surgical and radiation treatment, although inadequate, will increase the length of patients' survival as calculated from the first symptom of melanoma (cfr. 48). In spite of very large standard deviations for the average values, and although corrections for normal death rates were omitted, this statement seems justified with reference to patients admitted in Stage I and II. As to the length of survival in untreated Stage III patients, including those who obtained insignificant palliative irradiation, the figures tend to

Table XIII

Life Expectancy in Non-Cured Melanoma Patients

Average duration in months from first symptom of melanoma to death in tumour as calculated from failures only. Comparison between treated and untreated (Stage III) patients.

Black	treated	Stage I	58 months
	»	II	37
	not treated		33
Brown	treated	Stage I	67
	»	II	27
	not treated		17
Blue or *purple*	treated	Stage I	35
	»	II	35
	not treated		14
Red, pink or *skin-coloured*	treated	Stage I	51
	»	II	31
	not treated		12.8 months

indicate a shorter survival period in non-pigmented melanomas than in the pigmented ones (Table XIII).

Considering possible growth accelerating factors most authors stress the rôle of trauma; however that may be, it would be difficult to gain support for such an opinion from our clinical material. On the other hand, the impression was gained that the tumour process is definitely accelerated by *pregnancy* (cfr. 5).

This series includes six women, who either observed their melanoma during pregnancy, or became pregnant during treatment. All ran a rapidly fatal course. One of these had been free of symptoms for 6 years, and then latent metastases became vitalized during pregnancy. As well as in some other human carcinomas, pregnancy is thus considered as a serious complicating and accelerating factor, which should be avoided. Only one woman, radically operated several years previously and free of symptoms, has survived child-bearing.

Discussion

During the period under question we have been fortunate to receive a large number of early melanoma cases, and this explains our high cure rate in Stage I patients (Table VI) as well as the good end-results (Table IV). The analysis illustrates that the methods under question are on the whole satisfactory for local treatment of very early cases, but give poor results in dealing with lymph node involvement (Tables X—XII). It seems therefore mandatory to change those treatment methods in order to improve the cure rate. Before going into details, I want to stress that suggestions herein made are merely considered as presumptive plans, the effects of which cannot at present be substantiated by material from the Radiumhemmet.

It need hardly be emphasized that future plans must pay due consideration to the biological characteristics of the melanoma cells, above all to their capacity of *very rapid* penetration of vessels and lymph node barriers. This will at once rule out all time-consuming treatment methods. This implies further that in evaluating treatment methods we are not justified to compare results gained in melanoma with common slowly growing and invading carcinomas. If comparisons can be made they should be made with tumour types showing similar biological characteristics. *Time* seems thus to be an important factor. A sound principle of oncology says, that it is safer to be in advance of the tumour process than behind.

The primary melanomas should be treated as a *surgical emergency* and the widest possible block excision should be performed. Any method can be used — surgical or electrosurgical — provided the radical eradication of all tumour tissue is rapidly secured, including the removal of the deep subcutaneous lymphatic drainage. Radiological treatment is considered unsafe, and time-consuming, and will only give cures in selected early cases. In suitable cases classified as Stage I, no surgeon should desist from early amputation of fingers, toes, or the external ear. The

principles for wide dissection and management of subsequent defects belong in the field of surgery (cfr. PACK *et al.*).

With reference to our methods up to 1943 it seems advisable to leave the conservative excisions, which are only considered justified in very early cases. Due to present inability in determining the extent of lymphatic permeation it should be safer to apply wider dissections, and these are expected to diminish the risk of recurrences and metastases. How large the actual increase in cure rate would be in a material like ours is to date impossible to estimate.

The matter of dispute is what to do with the regional gland involvement appearing in Stage I patients. Present methods have salvaged 5 cases only in our series (Table XI). By means of so-called prophylactic gland dissection an additional number of patients would most likely have been living and well. In a series of Stage I cases devoid of clinical nodes, and yet subjected to preventive dissections, PACK & LIVINGSTON found minute metastatic foci, undetectable by common clinical methods, in *50 per cent.* This constitutes a strong argument in favour of preventive dissections before the appearance of palpable nodes. Conclusive reports concerning the actual gain in cure rate by adopting this method have so far not been published. In 1946, PACK, PERZIK & SCHARNAGEL (54) only stated a considerable increase in salvage in a small number of cases operated.

With reference to our stock of patients, prophylactic gland dissection would have implied unnecessary dissections in 60 patients during the 15-year period under question. An average of 4 patients a year would have been no extra burden to our co-operating surgical departments.

With a view to improvement of cure rate in Stage I melanomas *it seems thus advisable to join previous authors* (1, 9, 25, 28, 33, 34, 45, 52—54, 66) *in recommending prophylactic gland dissection in all suitable cases.*[1]

Before leaving the prophylactic gland dissection it should be emphasized that this method is not applicable to melanoma situated »*in the midline of the face or chest for which a bilateral neck dissection or a bilateral axillary dissection would have to be carried out*» (1). — From surgical and pathological points of view, prophylactic dissections seem, however, to be of doubtful value as regards melanomas of the distal part of the extremities, because part of the lymphatic drainage is passing into deep lymphatics, where melanoma cells might lodge. This might be more or less eliminated by the latest recommendations by PACK to perform the subsequent gland dissection a few weeks after the operation of the primary melanoma.

Turning to Stage II patients our results of treatment are very poor and even a small increase in cure rate would be acknowledged. Un-

[1] Confer the following recommendations by ACKERMAN & REGATO: »*When the tumor is located in an area from which the lymphatic drainage is predictable, a radical dissection of the anticipated metastatic node areas is mandatory*, in spite of the fact that the nodes may not appear clinically involved.» (1, p. 180.)

fortunately, possible improvement cannot be expected to be very large, because the filtering glands seem to be too rapidly passed by melanoma cells, as mentioned above. In the management of our material up to 1943, we have not paid sufficient regard to melanoma as essential emergency cases (Table XII). It would thus be possible to change our plan of gland treatment to immediate gland dissection and subsequent massive postoperative irradiation. In suitable locations, some not too advanced cases would most likely be salvaged by more radical surgery without undue delay: *earliest possible block dissection of both primary tumours and regional glands »in continuity»* according to PACK, SCHARNAGEL & MORFIT. If this should be done »in continuity» or as a two-step intervention depends upon both the site of the primary lesion and the routes for tumour emboli (1).

If the primary is located on the head, neck or trunk, the suggested operations leave very little to be desired so far radicality is concerned. Melanomas of the extremities will have to be treated by amputation (cfr. 52, 53, 55). These more radical interventions have to be tried and evaluated. They are in accord with the principles for the usual mastectomy for mammary carcinoma according to HALSTED (1894), and the method used for the eradication en bloc of rectal carcinoma (MILES), which methods have provided large increase in cure rate. Why should not similar good results be obtained in patients with malignant melanoma? — PACK stated in 1947 (55), that *by applying such wide local excisions of the primary melanomas plus regional gland dissection »in continuity», the cure rate was increased by 600 per cent* in comparison with the cure rate previously gained by conservative surgery in combination with radiation. A detailed report of end-results in melanoma is consequently expected from the Memorial Hospital.

To sum up, it seems to me advisable to concentrate most of our attention firstly to the treatment of *Stage I* patients by adopting (1) *Wider excision of primary melanoma*, and (2) *Routine preventive dissections of regional glands*, and further to apply (3) *earlier and more radical surgical interventions* to our *Stage II* patients. This program implies much attention and interest on the part of our colleagues in surgery. Concurrently, continued education of physicians and medical students will keep their mind open to the early diagnosis of melanoma and to the possibilities of radical treatment at our cancer centers.

Conclusions

Present treatment results and pertinent biological characteristics of malignant melanoma, such as early and marked invasiveness, affinity to the vascular system, marked loss of cellular cohesion, and rapid per-

meation of lymph glands, converge to the view, that time is one of the most important factors for successful management of malignant melanoma. Current trends in oncologic surgery towards more active and radical methods are in keeping with this and seem to be justified. The results herein reported are based on conservative surgical and electrosurgical interventions in combination with radiotherapeutical measures, which methods are on the whole directed to treatment of clinically established lesions. Our interventions have thus until now been behind the tumour process. This fact is substantiated by the present poor prognosis recorded in patients with tumour spread beyond the primary focus.

In order to improve the curability it would be wise to join previous authors in adopting prophylactic surgical interventions to predictable regional glands in all Stage I patients, and further to adopt more radical surgical methods without any delay to manifest lymph nodes and other satellite lesions in Stage II patients. These suggestions conform with present principles for treatment of mammary and rectal carcinoma, and have, moreover, been reported by previous authors to give improved cure rates. Radiological treatment in its present state should for preoperative suppression of growth be directed to regional nodes with questionable operability, and is further of palliative value.

The previously known disparity in malignancy between prepubertal melanomas and those in adults was corroborated, and this suggests that melanoma cells are under hormonal influence, which is further supported by the pronounced increase in malignancy observed during pregnancy.

SUMMARY

Out of 341 patients with cutaneous malignant melanomas 291 verified cases (85.3 per cent) were admitted to treatment at the Radiumhemmet during a 15-year period from 1929 through 1943. Thanks to our close follow-up service complete records brought up to December 1948 were available for analysis. In spite of its limitations, clinical staging with reference to the extent of disease at admission is considered of prime importance for the evaluation of results. Data regarding the incidence, distribution, precursory lesions, modes of growth, and differential diagnosis, etc. have been cursorily mentioned. Present treatment methods characterized by conservative surgical interventions partly in combination with radiological treatment have in this material provided the following uncorrected cure rates: Net five-year cure rate (conventional) 34.6 per cent; End result at 1948 in determinate group 30.8 per cent; Over-all end result at 1948 23.7 per cent.

The opinion is forwarded that more patients would probably be salvaged by wider and earlier surgical intervention, and in particular by prophylactic gland dissection in Stage I patients.

ZUSAMMENFASSUNG

Von 341 Kranken mit malignen Hautmelanomen wurden 291 verifiierte Fälle (85.3 %) in der fünfzehnjährigen Zeitspanne 1929—1943 in der Radiumklinik behandelt. Dank unseres genauen Nachuntersuchungssystems lagen vollständige Berichte bis Dezember

1948 zur Analyse vor. Trotz ihrer Begrenzungen hält Verf. die klinische Einteilung nach der Ausdehnung der Krankheit bei der Aufnahme für sehr bedeutungsvoll für die Berechnung der Ergebnisse. Angaben über die Verteilung der Häufigkeit, voraufgehende Erscheinungen, Wachstumsarten, Differentialdiagnose usw. werden kurz erwähnt. Die heutigen Behandlungsmethoden, die sich durch konservative chirurgische Eingriffe, teilweise mit Strahlenbehandlung kombiniert, auszeichnen, haben in diesem Material folgende unkorrigierte Heilungszahlen ergeben: Reine fünfjährige Heilungszahl 34.6 %; Endergebnis 1948 in bestimmter Gruppe 30.8 %; gesamtes Endergebnis 1948 23.7 %.

Es wird die Ansicht ausgesprochen, dass durch weitgehenderes und früheres chirurgisches Eingreifen und ganz besonders durch prophylaktische Ausschälung der Drüsen bei Kranken im I. Stadium wahrscheinlich mehr Patienten gerettet werden könnten.

RÉSUMÉ

Sur 341 malades atteints de mélanomes malins de la peau 291 (85.3 %), dont le cas fut vérifié, ont été admis au Radiumhemmet pour traitement, pendant la période de 15 années allant de 1929 à 1943 inclusivement. Grâce à notre excellent service de contrôle posthospitalier des observations complètes, tenues à jour jusqu'à décembre 1948, étaient disponibles pour l'analyse du matériel. En dépit de ses imperfections, le système de la répartition en stades cliniques d'après l'étendue de l'affection lors de l'hospitalisation est considéré comme étant d'importance primordiale pour l'évaluation des résultats. Les données concernant la fréquence et la distribution des tumeurs, les lésions préexistantes, les modalités de l'accroissement, le diagnostic différentiel, etc., ont été mentionnées en passant. Les méthodes actuelles de traitement, caractérisées par des interventions chirurgicales conservatrices partiellement combinées avec la radiothérapie, ont dans ce matériel donné le pourcentage — non corrigé — que voici de guérisons: pourcentage net de guérisons après cinq ans (conventionnel), 34.6 %; résultat final en 1948 par groupe déterminé, 30.8 %; résultat final général en 1948, 23.7 %.

L'opinion est émise qu'on sauverait probablement davantage de malades par une intervention chirurgicale plus étendue et plus précoce, en particulier par la dissection prophylactique des ganglions chez les sujets du stade I.

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FROM THE ORTHOPEDIC CLINIC OF THE CAROLINE INSTITUTE, STOCKHOLM, SWEDEN
(CHIEF: PROFESSOR STEN FRIBERG)

THE MYELOGRAM FOLLOWING OPERATION FOR HERNIATED DISC[1]

by

Folke Knutsson

The myelographic diagnosis of herniated disc is based on the pressure effect made by the prolapse on the contrast filled dural sac. The operative procedure in herniation of the disc consists of incision of the prolapse and extirpation of the detached fragments of the degenerated disc substance. After termination of the operation the surgeon can establish the disappearance of the protrusion of the disc substance. At a subsequent myelography the indentation into the dural sac should accordingly in such cases have disappeared. I have been able to establish that this is the case in several instances (Figs. 1—4).

Not in all cases, however, does the myelogram subsequent to operation regain an entirely normal appearance. A total extirpation of the herniated disc may be difficult to accomplish owing to adhesions or other complicating factors. The operation may be complicated by hemorrhage, leading to cicatrization and adhesions. At the subsequent myelography there may in such cases be present a deformation of the dural sac which entirely is to be attributed to the operation performed (post-operative deformity). In such cases it may be difficult or impossible to determine whether the deformation exclusively is post-operative in nature, being due to indurations and adhesions, or whether there is question of a recidivation of the herniation with a pressure effect on the dural sac.

I have had three cases in which the post-operative deformation had such an appearance that one had to take into consideration the possibility of recidivation of the herniation with impression in the dural sac. At operation, however, there was in no instance found a herniated disc, but merely post-operative cicatrization. This experience thus is an incitation towards caution in making the differential diagnosis (Figs. 5—7).

[1] Submitted for publication, June 4, 1949; read at the meeting of the Northern Association for Medical Radiology, June 1949.

Fig. 1.

892/48 *Myelography* 13. 4. 48: Impression in dural sac at the level of disc L: V—S: I.

Operation 15. 4. 48: Extirpation of herniated disc L: V—S: I. At myelography 13. 9. 48 the impression has disappeared.

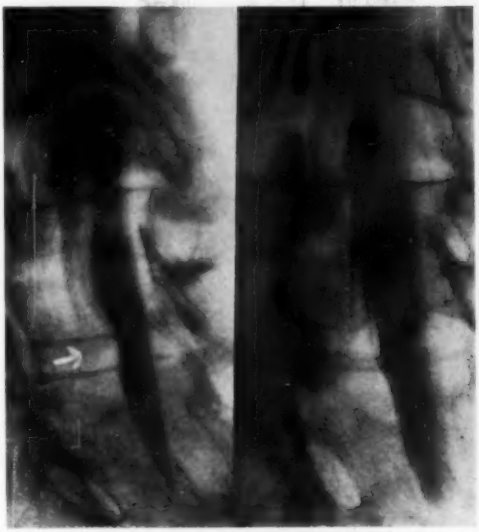

Fig. 2.

4905/48 *Myelography* 10. 11. 48: Impression in the dural sac at the level of L: V—S: I and to a lesser degree at the level of L: IV—L: V.

Operation 12. 11. 48: Extirpation of herniated disc L: V—S: I. Impression in the myelogram at the level of disc L: IV—L: V was caused by general protrusion of the disc but there was no herniation at this site.

At myelography 24. 1. 49 both impressions have disappeared.

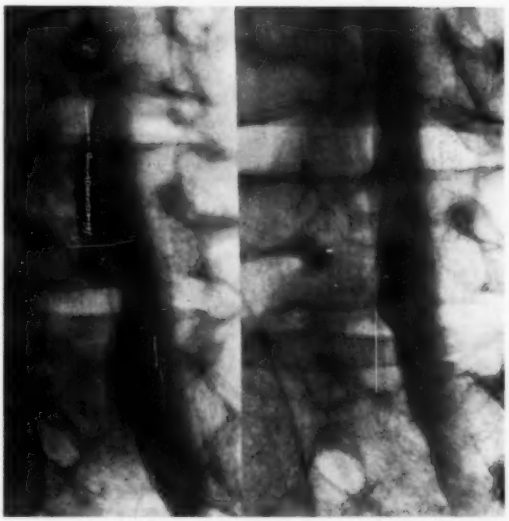

Fig. 3.

2591/45 *Myelography* 17. 5. 45: Impression in the dural sac at the level of disc L: V—S: I. *Operation* 18. 5. 45: Extirpation of herniated disc L: V—S: I. At myelography 22. 6. 45 the impression at the level of disc L: V—S: I has disappeared.

Fig. 4.

1265/47 *Myelography* 3. 3. 47: Impression in dural sac at the level of disc L: V—S: I. *Operation* 5. 3. 47: Extirpation of herniated disc L: V—S: I. At myelography 13. 12. 48 the impression has disappeared.

5724/45 *Myelography* 27. 12. 45: Impression in dural sac at the level of disc L: V—S: I.

Operation 7. 1. 46: Extirpation of herniated disc L: V—S: I. At myelography 1. 7. 47 there is present an impression in the dural sac at the level of disc L: V—S: I, which is interpreted as disc herniation.

At operation 3. 7. 47 there was not found any herniation at the old site, correspondent to the change in the myelogram. The nerve S: I was free and movable, the defect in the myelogram was obviously due to post-operative cicatrization.

Fig. 5.

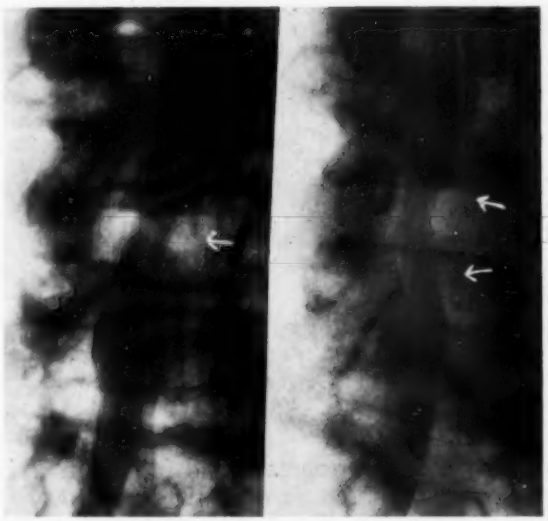

Fig. 6.

6194/48 *Myelography* 12. 11. 48: Impression in dural sac at the level of disc L: IV—L: V.

Operation 17. 11. 48: Extirpation of disc herniation L: IV—L: V. At myelography 9. 12. 48 there appears an extensive and deep defect in the myelogram at the level of disc L: IV—L: V, which is interpreted as a pressure effect from a recidivation of disc herniation.

At operation 13. 12. 48 there was found no herniation but merely scar tissue and adhesions.

Fig. 7.

4888/46 *Operation.* May 1946: Extirpation of disc herniation L: IV—L: V. At myelography 9. 4. 48 there was observed a large impression in the dural sac at the level of disc L: IV—L: V which was interpreted as disc herniation. At operation 15. 3. 48 there was not found a herniation but merely cicatrizations and indurations around root L: V at the level of disc L: IV—L: V.

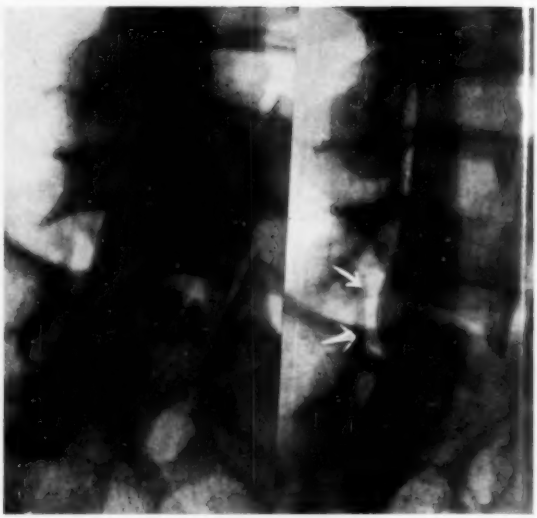

Fig. 8.

2598/45 *At myelography* 29. 6. 45 there appears a hernia-like protrusion of the dural wall in the posterior lateral portion at the level of disc L: V—S: I, owing to extirpation of ligamentum flavum at operation for disc herniation 25. 5. 45. On a comparable picture, taken prior to operation 22. 5. 45 the outline is smooth.

An entirely typical post-operative deformation arises following extirpation of ligamentum flavum, which is carried out by the surgeon in order to approach the disc. The dural wall is adjacent to ligamentum flavum and on extirpation of the latter there occurs a local hernia-like protrusion of the dural wall in the correspondent area, *i. e.*, in the posterior lateral area (Fig. 8).

SUMMARY

Subsequent to operation for herniation of the disc the impression in the dural sac caused by the prolapse often disappears and the myelogram assumes a physiological appearance. In certain cases, however, owing to cicatrization following the operative procedure, there remains a post-operative deformation of the dural sac. The change in the myelogram caused hereby can in many cases not be differentiated from that caused by recidivation of the herniation.

ZUSAMMENFASSUNG

Nach einer Operation wegen Zwischenwirbelscheibenprolaps verschwindet oft die vormalige, durch den Prolaps bedingte Impression des Durasackes, und das Myelogramm nimmt ein normales Aussehen an. In gewissen Fällen bleibt jedoch durch Narbenbildung nach der Operation eine post-operative Deformierung des Durasackes zurück. Die hierdurch bedingte Veränderung des Myelogramms lässt sich in vielen Fällen nicht von einer durch ein Prolapsrezidiv verursachten unterscheiden.

RÉSUMÉ

Après l'opération de la hernie discale on voit souvent disparaître l'encoche du sac dural qui avait été conditionnée par le prolapsus, et le myélogramme reprend un aspect normal. Dans certains cas, cependant, il persiste une déformation postopératoire du sac dural, due aux cicatrices laissées par l'intervention. Les modifications qui surviennent de la sorte dans le myélogramme ne peuvent, souvent, être distinguées de celles causées par une récidive de la hernie.

FROM THE RADIOLOGIC CLINIC IN LUND, SWEDEN (THE THEN HEAD: PROF. LARS EDLING AND FROM RADIUMHEMMET IN STOCKHOLM (HEAD: PROF. ELIS BERVEN).

SHORT-DISTANCE LOW-VOLTAGE ROENTGEN THERAPY OF INFLAMMATORY CONDITIONS IN THE TONSILS[1]

by

Sven Hultberg.

In irradiation therapy of inflammatory conditions in the tonsils, a distinction has to be made between a) the treatment of acute tonsillitis — angina, and b) irradiation of chronic inflammatory conditions with hypertrophy of the tonsils. In the latter instance, the aim is to cure the chronic tonsillitis, bring the tonsils to shrivel and, above all, by this treatment to prevent the continual recurrence of acute anginas with all the risks that they involve to joints, heart, kidneys, etc. — It is, of course, also an advantage that the regression of the tonsils simultaneously relieves the patient of any troubles of a mechanical kind, such as hinder deglutition and respiration, that may have been caused by the hypertrophy.

The *acute, high-febrile anginas* are but rarely submitted to irradiation. The patients are, as a rule, treated at home. However, when complications of some kind or other have occurred and the patient, consequently, has been admitted to a hospital, we — at Radiumhemmet — fairly often find such patients sent to us, this notwithstanding modern chemotherapeutics. Our colleagues of the Ear, Nose and Throat Department have come to value the help that roentgentherapy may offer in these cases. Small doses of only 15—25 r on the skin, administered with 180 kV. and $^1/_2$ mm Cu + 1 Al-filter at a focal—skin distance of 40—50 cm, often have a strong mitigating effect on the inflammatory condition, producing considerable relief, after only a few hours, from the patient's subjective troubles. As a matter of course, any form of near distance therapy will prove without avail in these cases, not least owing to the fact that these

[1] Read at the meeting of the Northern Association for Medical Radiology, Stockholm, June 10—12, 1949; submitted for publication, June 27, 1949.

patients are not seldom affected with a pronounced trismus that prevents the introduction of an applicator into the oral cavity.

On the other hand, cases of *chronic tonsillitis*, and of marked hypertrophy with ugly, purulent plugs, as well as cases of continually recurrent anginas constitute a much wider, and exceedingly fruitful, field for investigation. As early as in 1911, MENZEL in Vienna described a case that he had successfully treated with roentgen. In 1913, NOGIER and REGAUD presented another report and, in 1921, came WITHERBEE's account of 500 cases. GLAUNER, in 1940, in his book entitled »Die Entzündungsbestrahlung», warmly recommends irradiation in these conditions, as does also BULL ENGELSTAD in his work »Stråleterapi», issued in 1946. — The application of radium to the tonsils was tried in 1917, in Sweden, by HOLMGREN and BERGGREN, independently of one another. BERVEN's invaluable report was published in 1923, concerning a detailed description of 150 cases treated with a specially constructed radium instrumentarium.

External roentgen therapy, as well as *local radium application*, gave satisfactory results with intended effect. Various authors record healing in 30 to 90 per cent; mostly 70—90 per cent. At external roentgentherapy, generally doses of 3—4 × 100—250 r were applied to either side of the pharynx with a $^1/_2$ mm Cu + 1 mm Al-filter, with 150—180 kV. and at a focal—skin distance of 30—50 cm. This dosage usually sufficed for overcoming the infection somewhat, but was not always strong enough to bring about a noteworthy regression of the tonsillar hypertrophy which requires a bigger dose, administered locally to the tonsil itself. As demonstrated by BERVEN, this could be adequately accomplished by means of radium. If a similar dose of roentgen were applied from without, the intermediate tissues would run a risk of being injured, particularly when children and young people are concerned. Accordingly, a roentgentherapy was tried, using special applicators directed straight at the tonsils. Still, the adjustment of these tubes with an ordinary roentgen apparatus will be rather a complicated and awkward matter. In 1940, when we in Lund were in a position to start working with Philip's short-distance low-voltage plant, the author realized that this should also be suitable for the treatment of tonsils. A brief description of the first attempts was published in 1943. — In 1947, CALVET mentions a method of dealing with these affections by means of the Siemens short-distance low-voltage apparatus, applying doses of 4—6 × 500 r once a week. Each irradation lasted for approximately 5 minutes. He states that the healing results were good in 50 per cent of his cases, the effect being unfavourable in 30 per cent. During the years 1942—46, CALVET had treated 72 cases in this way.

The number of cases that I have to report is small owing to the fact that I wished first to wait a few years to gain experience. In 1941, 6 cases of chronic tonsillitis and strongly hypertrophic tonsils were given contact therapy. Two of these cases concerned 16-year-olds, one was 80 and the remaining three between 38 and 50 years of age. They all had throat troubles of several years' standing with frequent, recurrent anginas and pharyngeal catarrhs. They also manifested considerable hypertrophy, sometimes with ugly, plugged and cleft tonsils, the size of a biggish walnut. The Waldeyer ring, too, showed not seldom a hypertrophy and a muco-purulent cover.

After previous local anaesthesia, performed with a 2 per cent pantocain or tetracain solution with a spray apparatus, the applicator was introduced down towards the tonsil, the tube was inserted, and then the irradiation could be performed without any difficulty and without causing any particular discomfort to the patient. At first, we counted on requiring only to give one single irradiation, applying doses of between 1,200 and 2,200 r, depending on the size of the tonsils. These doses corresponded to an irradiation time of only 20—40 seconds. The distance equalled 4 cm and no additional filter was used. This gave a depth dose to $^1/_2$ cm of approximately 50 per cent of the superficial dose, and to 1 cm of about 25 per cent of the same dose. The tube is operated at 50 kV. and 2 mA. For a detailed description of the apparatus, the method of treatment and depth dose curves, reference may be had to the Acta Radiologica, Supplement LIV, 1943.

On the very first day of treatment, shortly after the irradiation, the patient disclosed a moderate edema in the tonsillar region. However, it disappeared within 12 to 24 hours. About 8—10 days later, a reaction set in, with a sore feeling when swallowing and painful throat, as at mild angina or pharyngitis, though with no temperature. In the course of a week, a fibrinous epithelitis was observed on the tonsillar surface. In one case, given a dose of 2,200 r, these troubles continued for about two weeks.

Two of these six patients were given three irradiations in all at intervals of 2 to 4 months, in the one case being directed only at a remaining hypertrophic tonsil on one side. At a check-up five years later, it was found that all had been relieved of their recurrent anginas ever since the first treatment. The additional doses administered in two cases had, in all likelihood, been superfluous, since the inflammatory condition in the tonsils, and not the hypertrophy, represents the essential factor in this connection and it had already healed after the first irradiation in all these cases. Even the hypertrophy showed a distinct regression.

During 1947 and 1948, I had four patients suffering from severe tonsillitis under treatment at Radiumhemmet. The age was between 9 and

7 years. Two of them appeared with rather acute symptoms and were, n the first place, given the usual resorption irradiation of both sides of the hroat, with a total dose of up to 600 r during 10—12 days — applied o the skin. Their symptoms were mitigated but, a few months later, hen this therapy was found to be insufficient for complete recovery rom the chronic inflammatory condition, contact therapy was added. In order to avoid, if possible, the rather troublesome, though not serious, i radiation reaction produced by the single treatment, I instead applied 3 × 500 to 600 r with 2—3 days' interval between each treatment. The reaction in this way became much milder and the final result nevertheless satisfactory with atrophy of the tonsils and complete regression of the inflammatory condition. At a check-up 8 months to $1^1/_2$ year afterwards, it was established that also these four patients had been spared from falling a victim to tonsillitis ever since the treatment, and the tonsils had considerably decreased in size, being in most of the cases entirely atrophied. Thus, the intended result had been achieved in all ten cases. Even an ev. hypertrophy of the Waldeyer ring and a pharyngitis showed a remarkable improvement, though only the tonsils were irradiated upon.

A dose of 500 to 600 r requires only 10 to 13 seconds irradiation. This renders this form of treatment much easier to carry out than the other methods of intraoral therapy hitherto applied. It is more effective than roentgentherapy from without. Furthermore, since it does not involve surgery and is harmless, I consider that it deserves to be tried to a much greater extent than has so far been done and not merely in cases where a contra-indication may be present against surgical therapy. If the patients live far away, a fractionized treatment may be inconvenient. In such cases a single dose may quite well be administered of 1,000 to 1,200 r with otherwise the same irradiation conditions, viz. a focal—skin distance of 4 cm and no additional filter. The applicator may have a diameter of 2—3 cm.

SUMMARY

The favourable results of short-distance low-voltage roentgen therapy are reported in ten cases of chronic tonsillitis treated during the years 1943—1948. The author suggests that the method be tried to a greater extent than hitherto, with doses of 2 to 3 × 500 r, 50 kV, 2 mA, 4 cm focal—skin distance, and no additional filter. Each treatment will then take only about 10 seconds and is technically easy to perform.

ZUSAMMENFASSUNG

Die günstigen Ergebnisse von Röntgennahbestrahlung bei zehn Fällen von chronischer Tonsillitis, die in den Jahren 1943—1948 behandelt wurden, werden wiedergegeben. Verf. schlägt vor, dass die Methode in grösserem Ausmasse als bisher versucht

wird, und zwar mit einer Dosierung von 2—3 × 500 r, 50 kV, 2 mA, 4 cm Fokus—Haut-abstand, ohne zusätzliches Filter. Jede Behandlung wird dann nur etwa 10 Sekunden dauern und technisch leicht ausfürbahr sein.

RÉSUMÉ

Rapport sur les résultats favorables obtenus dans dix cas d'amygdalites chroniques traitées par la radiothérapie à courte distance et bas voltage pendant les années 1943—1948. L'auteur suggère que la méthode soit essayée sur une plus grande échelle que jusqu'ici, avec des doses de 2 à 3 × 500 r, 50 kV, 2 mA, et une distance de 4 cm du foyer à la peau, sans écran additionnel. Ainsi chaque séance du traitement ne durera qu'environ 10 secondes et sera d'une technique facile.

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SUPPLEMENTARY REMARKS TO ARTICLE ON SCHÜLLER-CHRISTIAN'S DISEASE[1]

Acta Radiologica 30 : 279, 1948

by

Åke H. Mellbye

THOMAS ROSENDAL has drawn my attention to the great similarity between my case 1 and several of the cases of neurofibromatosis Recklinghausen, which he recorded in Acta Radiologica 19: 273, 1938. The appearance of my patient resembles very much that of his patients as well as several of the cases published in the literature. The case has been taken up for renewed perusal, therefore.

The pouch-like soft swelling in the right temporal region demonstrates great similarity to elephantiasis neuromatodes. In my case, however, there is no anomalies of pigmentation as generally noticed in neurofibromatosis. With regard to skeletal changes in neurofibromatosis, such are observed as a rule where the skin is affected, and they are localized to one side as a rule, as in this case. In this case, however, there is an additional destruction in the contralateral maxilla. Destructions on the base of the skull with localization more especially to the middle cavity of the skull and to the orbital base, as also enlargement of the sella, have been described several times previously. Such an extensive destruction posteriorly in the calvarium as the present one is not usual, however, though conceivable at any rate. Also the other destructions observed are consistent with neurofibromatosis. On the whole there is no objection against this case being neurofibromatosis. The decisive factor must be whether the histological examination supports this diagnosis. The specimen has again been submitted to Professor L. KREYBERG, and he expressed the opinion that in this case it may be a neurofibroma or a neurinoma with slow growth and with remnants of lipoid macrophages. According to this the diagnosis *Neurofibromatosis Recklinghausen* must be considered probable.

[1] Submitted for publication, May 16, 1949.

SUMMARY

Case 1 in the author's article in Volume 30, Fasc. 4—5 may be a case of Recklinghausen's disease. The control examination of the histological preparations furnished evidence in support of this assumption.

ZUSAMMENFASSUNG

Fall 1 in Verf.s Arbeit in Band 30, Heft 4—5 kann ein Fall von Neurofibromatosis Recklinghausen sein. Erneute Durchsicht des histologischen Präparats spricht für diese Diagnose.

RÉSUMÉ

Le cas 1 de l'article de l'auteur, Vol. 30, Fasc. 4—5, pourrait être une neurofibromatose de Recklinghausen. Le contrôle de la coupe histologique vient à l'appui de ce diagnostic.

FROM THE ROENTGEN DEPARTMENT, OSLO MUNICIPAL HOSPITAL, ULLEVÅL, NORWAY
(CHIEF: J. FRIMANN-DAHL, M. D.)

TUBERCULOMA — SIMULATING CARDIAC ANEURYSM OR LOCALIZED PERICARDIAL EFFUSION[1]

by

Kjell Liverud

On the normal roentgenograms of the chest, the heart and the mediastinal organs appear as a shadow between the air-containing lungs. In the routine radiographic practice the shadow is usually called the »heart shadow», the »mediastinal shadow» or the »medial shadow». Its contours are designated by names taken from ordinary anatomical terminology (for example: contour of left ventricle, arch of the aorta etc.).

Pathological changes in a particular section of a contour may therefore easily be ascribed to those organs which commonly form contours. Before beginning to make the diagnostic synthesis it should always be remembered that the boundary of the shadow is not formed, as the ordinary use of language might imply, by the aforesaid organs, but is the result of the difference in density between the air-filled lung tissue and the compact mass of tissue lying between the lungs, normally bounded outwardly by the medial, visceral pleura.

In pathological cases the boundary may be showed forward, both by the heart and the mediastinal organs and by effusions in the pericardium or pleura, or through pulmonary changes which lead to displacement of the air-containing tissue.

In other words, an altered »heart shadow» does not necessarily denote a change in the heart itself.

The greatest diagnostic difficulty in such cases may be the actual diagnosis of the location: To what organ is the pathological process to be assigned?

If the contour is assumed to have been formed by air-filled lung tissue, the extracardial processes (effusions, peripheral condensations in the lungs) are drawn within the field of diagnostic possibilities. This mode of consideration may save us from erroneous diagnoses.

[1] Submitted for publication, May 7, 1949.

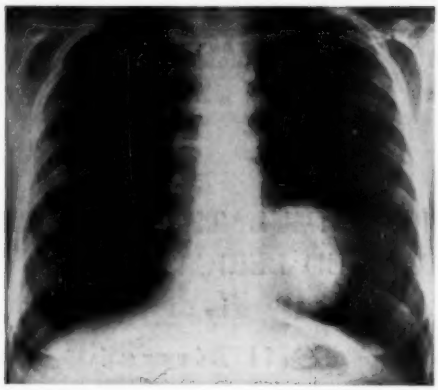

Fig. 1. Anterior teleradiograph showing large bulge of upper part of the left ventricle.

Fig. 2. Right oblique teleradiograph.

Fig. 3. Lateral teleradiograph.

As there is generally more to be learnt from wrong diagnoses than from diagnostic triumphs, the following case shall be described:

The patient was a woman aged 44, who in 1943 was admitted to the Ullevål Hospital Med. Dept. VIII. In the long history of her illness the following points are of importance:

In 1931: Pleurisy on the right side. Lay in bed for 4 months. Afterwards repeated medical examinations, without discovery of active pulmonary tuberculosis.

In 1936 she got a tuberculous abscess below the right costal arch. Cured by puncture treatment. Pus: Tbc +. WR ÷.

Was well until 1943, when she again got an abscess at the same place, with external fistula. The same year, 6 months later, she had symptoms of ascites and was admitted to the Med. Dept., where there was found polyserositis with severe ascites. Abundant fluid in both pleural cavities, so that the heart shadow was »drowned» in the exudate shadows at the level of the hilus. The patient recovered, and a roentgenogram taken on 22/2 1944, after the pleural exudates and the ascites fluid had been absorbed, gave occasion to many diagnostic considerations (Figs. 1, 2 & 3).

On the upper two-thirds of the contour of the left ventricle was seen a uniform, sharply defined expansion towards the surrounding clear lung tissue. The bulge passed smoothly over into the rest of the heart contour, without »incisura» (1, 19) or hypertrophic »humps» (4) in the adjoining part of cardiac wall. The density of the bulge was uniform, without calcifications, and was similar to that of the heart shadow, possibly a little less dense on hard-exposed pictures. Apart from the bulging portion, the shadow of the heart was not enlarged. The pulsations were regular, being well marked also at the site of the bulge, which seemed to follow the pulsations of the heart. On screening one got an impression that the systolic movements came a little later in the bulge (several observers). No perceptible change in the form of the bulge was found on deep inspiration or expiration. JANSSON's sign on the diverticulum of the pericardium was negative (13). Neither during fluoroscopy nor on radiograms taken in different projections could the bulge shadow be distinguished from the heart shadow.

Upwards in the right lung was seen a fibrous infiltration. Remains from pleural exudates could not be detected, but very small adhesions were found in both sinuses.

Diagnosis

Among the many differential-diagnostic possibilities one had to reckon with pathological processes in the heart and in the large vessels, tumours in the mediastinum (dermoid cysts), encapsulated exudates in pleura or pericardium and peripheral pulmonary affections. On the basis of the roentgenological findings the following diagnostic possibilities were considered to be the most obvious (Fig. 4):

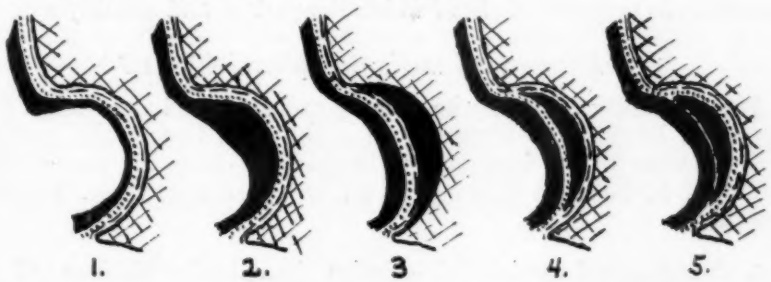

Fig. 4. Diagrammatic presentation of the most probable diagnostic possibilities.

1. Cardiac aneurysm. 2. Tumour of the heart. 3. Tumour of the lung. 4. Pleural localized effusion. 5. Pericardial localized effusion, »diverticulum» of the pericardium.

1. *Aneurysm of the cardiac wall.*

The picture may be said to resemble an illustrative case of cardiac aneurysm (2, 21), and if we take as criterion for a cardiac aneurysm a localized protuberance of the contour of the heart, with abnormal pulsations, this diagnosis seems to be naturally suggested. The diminished density of the shadow speaks neither for nor against this view, since the density of a cardiac aneurysm may vary from being the usual density of the heart to being hardly perceptible (20, 22). Meanwhile there were several things which in our opinion spoke against this diagnosis: An aneurysm is usually the last stage of an infarction occasioned by a coronary affection. Here there was found no enlargement of the heart, either on radiographic or on clinical examination. The patient had never had symptoms of coronary affection or of heart disease in any form. The apical impulse was not paradoxical (7, 3). The blood pressure had maintained normal values for many years, the electrocardiogram was normal, and we had no proof that the bulge was formed by the heart itself.

2. *Tumour in the heart or pericardium?*

Primary tumours at these places are very rare, and we had no grounds for supposing that the patient was suffering from some other malignant tumour, which might lead to metastases.

3. *Pulmonary tumour?*

This diagnosis was deemed improbable, at any rate as regards a malignant tumour. The shadow was quite sharply delimited, it was situated peripherally in the lung and no other signs of pulmonary or bronchial tumour, such as emphysema, atelectasis or the like, were present. It was found more reasonable to regard the changes as having connection with the polyserositis from which the patient had recently suffered.

4. *Encapsulated mediastinal-pleural effusion?*

The possibility could not be entirely excluded, and the clinical findings might be taken to support such a diagnosis. One would, however, have expected to see interlobary changes, but here the condensation seemed to be bounded laterally by an unbroken membrane. The next possibility:

5. *Encapsulated pericardial effusion* (pseudo-diverticulum of the pericardium) (14, 18, 10) might explain the sharp lateral delimination. It is probable that during the polyserositis the patient also had exudation in the pericardium. This would explain the close relation of the bulge

o the heart shadow. Encapsulated pericardial exudations are most often of rheumatic or tuberculous origin (8), and this patient had suffered from a tuberculous disease. Against such a diagnosis spoke to some extent the localisation (21.), but, on weighing the different diagnostic possibilities against each other and taking into account the radiographic and clinical findings and the history of the case, we arrived at this diagnosis.

(No clinical signs of cardiac concretion were present.)

As our department at that time had no kymograph, the patient was sent to another roentgen department for examination in this respect.

Kymographic examination showed: »Pulsations such as one expects to find in case of aneurysm, while it is difficult to imagine such a picture in case of encapsulated exudate in the pericardium.

Diagnosis: Probably aneurysm of the left ventricle.»

Thus we here have diagnosis standing against diagnosis.

The diagnosis of aneurysm of the cardiac wall was based exclusively on the roentgen findings: the localized bulge of the contour and the abnormal pulsations. These signs are regarded by many authors (5, 11, 15, 17) as being very characteristic of aneurysm. Abnormal pulsations on »silent» zones, however, occur also in case of pericardial changes (9) and pulmonary changes in the vicinity of the heart (5, 17, 7), so that we are warned against attaching too much importance to the pulsations (16).

We were therefore doubtful as to the evidential value of the abnormal pulsations, the more so because it is stated that pericardial diverticula often have post-systolic lateral pulsations. (8.)

Other methods for arriving at a more certain diagnosis were not employed. Puncture biopsy, perhaps with insufflation of air into the cavity (6, 12), was regarded as being a dangerous method to adopt for the purpose of excluding the possibility of a cardiac aneurysm. We abstained from bronchography, as the patient had recently suffered from a tuberculous affection, and there was little hope that such examination would clear up the situation. Diagnostic pneumothorax was not likely to succeed, as we had to reckon with the occurrence of pleural adhesions (see autopsy).

The solution of the riddle was obtained 16 months later, when the patient got an acute lung disease attended by high fever, with copious secretion of fluid in both pleural cavities (Tbc positive in exudate). The illness led to death in the course of one month.

Autopsy

Cause of death: Miliary tuberculosis in lungs, liver, spleen, pleura and peritoneum (cranium not opened).

Fig. 5. Anterior teleradiograph, showing density in the upper part of the left ventricle. Taken 8 years earlier, but then not assigned any importance.

Thorax: Trachea and bronchi: normal findings. Heart: 310 g. Somewhat flaccid and dilated. Normal valves, walls and coronary vessels. Thus there existed no cardiac aneurysm. Pericardium: Surface smooth and glossy. Contained 1,300 cc. of clear, serous fluid (certainly formed during the last illness). Accordingly there was likewise no encapsulated pericardial exudate or (pseudo-)diverticulum of the pericardium.

Left pleura: Half a litre of highly turbid fluid. Thickening of the pleura by 3 or 4 mm., adhesions at the base, over the apex and laterally at the back.

Likewise here there was no encapsulated pleural exudate that could have caused the bulge on the heart shadow.

Left lung: In the upper lobe, just below the hilus, was found a tumour the size of a fist, surrounded by a thin capsule of connective tissue. Medially it was separated from the pericardium by a cicatricial formation, 3—4 mm. in width, bounded posteriorly by the 1 cm. wide interlobar space. The tumour was of dark-red colour, of soft consistency, with granular cut-surface and necrosis in the hinder part.

Microscop. diagnosis: Poorly differentiated carcinoma (oat-cell carcinoma).

The result was not very flattering for us roentgen-diagnosticians. On re-examination of a chest-picture, taken 8 years earlier, there was found, however, a condensation in the upper part of the left ventricle (Fig. 5). Was the process so old? And could an oat-cell carcinoma develop so slowly?

The preparation was re-examined, with the result that there was found to have undoubtedly existed a tuberculous granulation tissue. The cause of the pathological »heart shadow» was a tuberculoma.

The case has made it abundantly clear that a localized bulge on the heart shadow cannot unreservedly be ascribed to the heart. Atypical pulsation in what appears to be a protuberance of the contour of the heart is not a pathognomonic roentgen-symptom of cardiac aneurysm. This symptom-complex may also occur in case of pericardial exudations (3) and in pulmonary changes with pleuropericardial adhesions (9, 5, 17, 7), and likewise, as here, in case of a medial, peripherally situated, tuberculoma.

The anamnesis and the clinical and roentgenological findings must be taken together in order to make the diagnosis more certain.

SUMMARY

A case is described in which a fist-sized tuberculoma with pleuropericardial adhesions simulates a cardiac aneurysm or a pericardial exudation. The diagnostic difficulties are discussed.

ZUSAMMENFASSUNG

Es wird ein Fall beschrieben, wo ein faustgrosses Tuberkulom mit pleuroperikardialen Verwachsungen ein Herzaneurysma oder einen Perikardialerguss vortäuscht. Die diagnostischen Schwierigkeiten werden erörtert.

RÉSUMÉ

Description d'un cas où un Tuberculome de la grosseur du poing, accompagné d'adhérences pleuro-péricardiques, simulait un anévrysme du cœur ou un exsudat du péricarde. Discussion portant sur les difficultés du diagnostic.

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